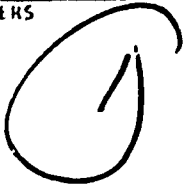



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ENANTIOMERICALLY PURE ACETALS IN ORGANIC SYNTHESIS:
RESOLUTIONS AND DIASTEREOSELECTIVE ALKYLATIONS
OF ALPHA-HYDROXY ESTERS

by
James Allen Fryling

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A Dissertation Submitted to the Faculty of the
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In Partial Fulfillment of the Requirements
For the Degree of
DOCTOR OF PHILOSOPHY
In the Graduate College
THE UNIVERSITY OF ARIZONA

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ABSTRACT

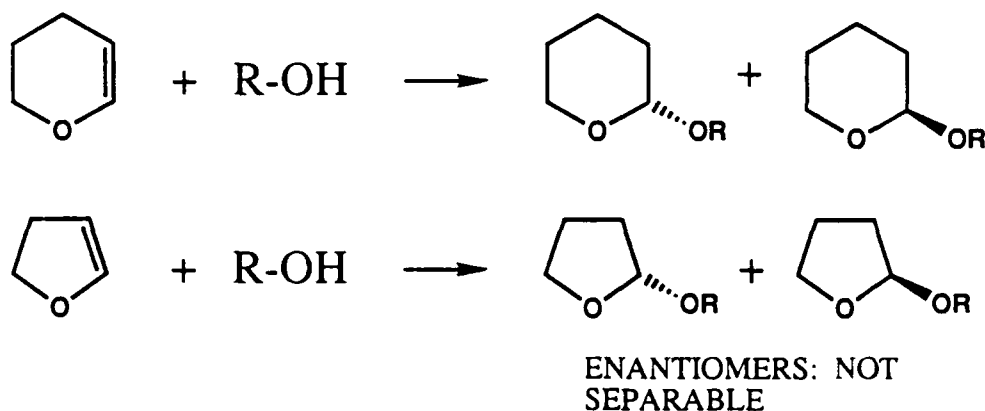
The diastereomeric tetrahydropyranyl (THP) and tetrahydrofuran (THF) ethers of a variety of α -hydroxyesters were synthesized and separated by column chromatography. The separability of the diastereomers was found to be a general phenomenon which allowed for wide variations in both the THP/THF ring and the α -hydroxyester. The resolved compounds could be deprotonated and alkylated diastereoselectively with a variety of electrophiles. The diastereoselectivity ranged from 1:1 to 12:1 depending on the α -hydroxyester, the alkylating agent, and the reaction conditions. In most cases the diastereomeric products of the alkylation were also separated by column chromatography. This alkylation method was used in the synthesis of the natural product (S)-frontalin and its enantiomer with optical purity. Modifications to the THP and THF rings were synthesized in an attempt to develop a "chiral THP". The (S)-methyl lactyl, (S)-methyl mandelyl, and (R)-pantolactyl 3-benzyloxytetrahydrofuranosides were synthesized and separated. Transacetalization to the methyl furanosides gave "chiral THF's" which were used in the resolution of other racemic α -hydroxyesters.

CHAPTER 1. SEPARABILITY OF α -HYDROXY ESTER TETRAHYDROFURANYL AND TETRAHYDROPYRANYL ETHERS.

The use of protecting groups is critical to the success of most syntheses of natural products and the quest for new protecting groups which have greater stability or more versatility is a continuing challenge. Likewise, intensive research is being conducted by numerous groups to develop methods which will allow for diastereoselective (or even diastereospecific) reactions to be performed so that compounds can be prepared in enantiomerically pure form. The logical combination of these two spheres of research is to develop a protecting group which would allow for diastereoselective reactions to be performed either on the protecting group itself or on the species under protection. In order to function in this manner the protecting group must be stable, easily prepared, and must have a chiral center which would direct the stereochemical course of subsequent reactions (achiral starting materials can only produce achiral or racemic products). A very likely candidate for just such a chiral protecting group is the tetrahydropyranyl (or tetrahydrofuran) ether.

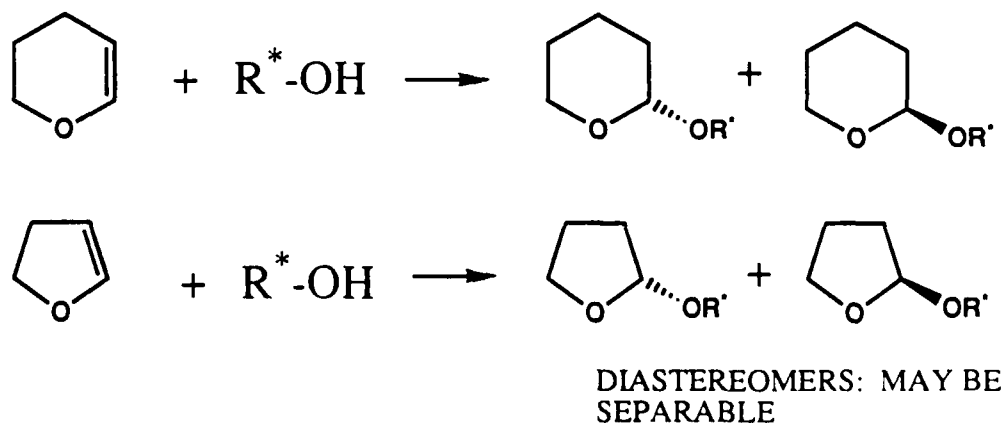
When an achiral alcohol is added to 2,3-dihydropyran (DHP) or 2,3-dihydrofuran (DHF) in the presence of an acid catalyst a pair of enantiomers is generated due to the formation of the chiral center on the tetrahydropyranyl (THP)

or tetrahydrofuranyl (THF) ring (Scheme 1). Since enantiomers



SCHEME 1. REACTIONS OF DHP AND DHF WITH ACHIRAL ALCOHOLS

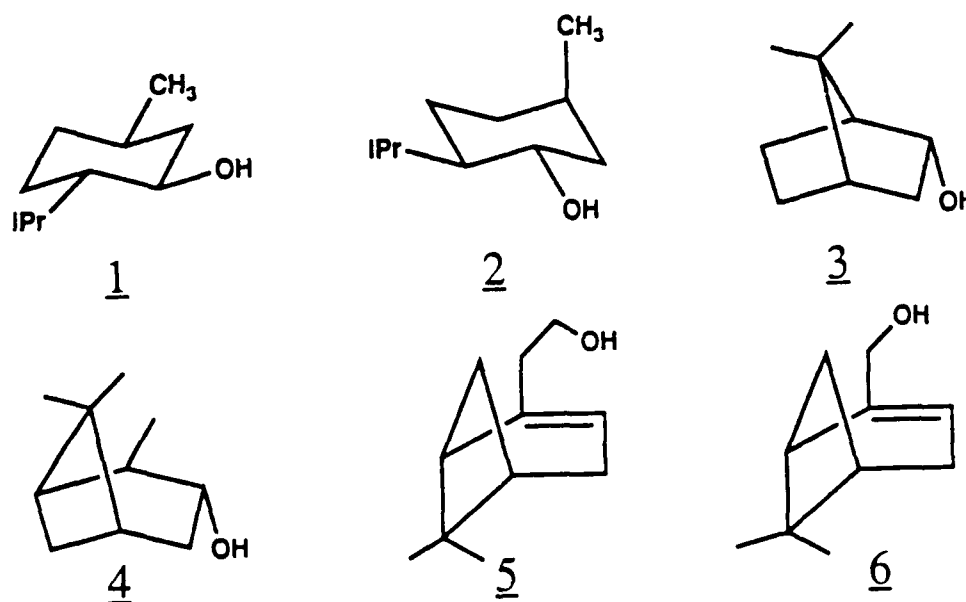
have identical physical properties (except for the direction they rotate plane polarized light) they are not separable by simple chromatography or crystallization. However, if an enantiomerically pure alcohol is similarly reacted with DHP or DHF (Scheme 2) then a pair of diastereomers is formed.



SCHEME 2. REACTIONS OF DHP AND DHF WITH CHIRAL ALCOHOLS

Diastereomers often have different physical properties and the potential exists for their separation.

A survey of the alcohols (Scheme 3) (-)-menthol 1, (+)-isomenthol 2, (-)-borneol 3, (-)-isopinocampheol 4, (-)-nopol 5, and (-)-myrtenol 6 demonstrated that none of these alcohols gave THP diastereomers which were separable on analytical silica gel tlc plates using mixtures of ethyl acetate and hexanes as eluent.



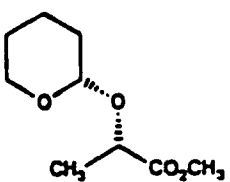
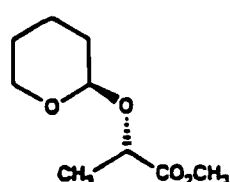
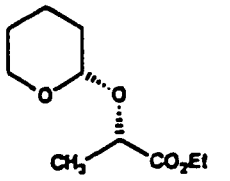
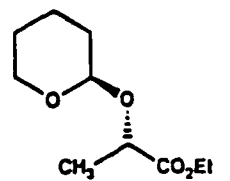
SCHEME 3: CHIRAL ALCOHOLS GIVING INSEPARABLE THP ETHERS

However, the diastereomeric THP ethers of (S)-methyl lactate were found to be separable on analytical tlc plates and also by column chromatography. In fact, the separability of the

THP and THF ether diastereomers was found to be a general phenomenon for a wide variety of α -hydroxy esters. As shown in Table 1 the separability of the diastereomers allowed for great variations not only in the α -hydroxyester that was used but also for variations in the THP or THF portion of the molecule as well.

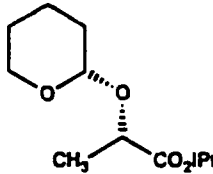
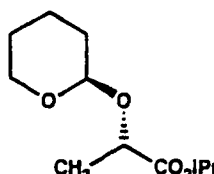
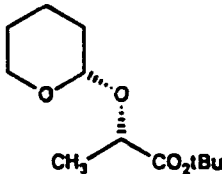
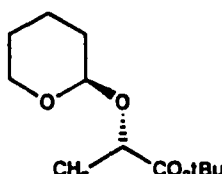
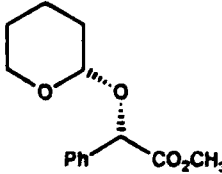
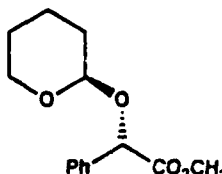
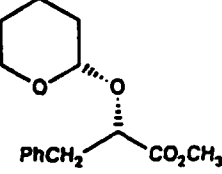
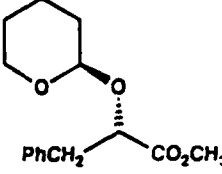
Table 1. Separation of Diastereomeric THP and THF

Ethers of α -Hydroxy Esters

<u>Entry</u>	<u>Diastereomeric Acetals</u>	<u>Yields^a, %</u>	<u>α^b(Solvent)^c</u>
1	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p><u>7a</u></p> </div> <div style="text-align: center;">  <p><u>7b</u></p> </div> </div>	49, 49	1.18 (20)
2	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p><u>8a</u></p> </div> <div style="text-align: center;">  <p><u>8b</u></p> </div> </div>	45, 38	1.18 (20)

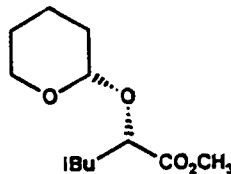
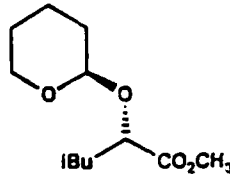
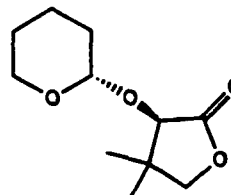
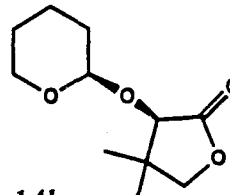
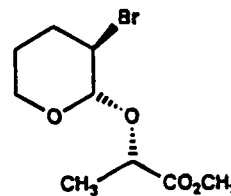
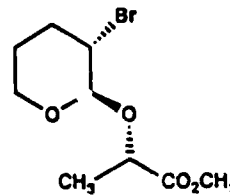
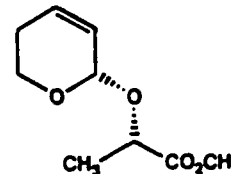
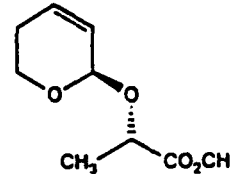
^aIsolated yields of the less polar (a) and more polar (b) diastereomers, respectively. ^bThe separation factor, α , is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). ^cSolvent is given as the percent ethyl acetate used in hexanes.

Table 1 (cont). Separation of Diastereomeric THP
and THF Ethers of α -Hydroxy Esters

Entry	Diastereomeric Acetals	Yields ^a , %	α^b (Solvent) ^c	
3	 <u>9a</u>	 <u>9b</u>	49, 45	1.12 (20)
4	 <u>10a</u>	 <u>10b</u>	75	1.07 (20)
5	 <u>11a</u>	 <u>11b</u>	42, 49	1.10 (20)
6	 <u>12a</u>	 <u>12b</u>	41, 51	1.11 (20)

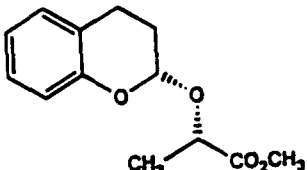
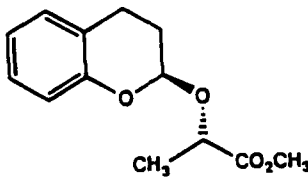
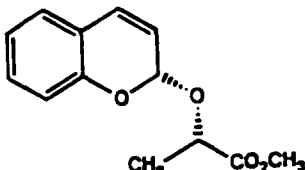
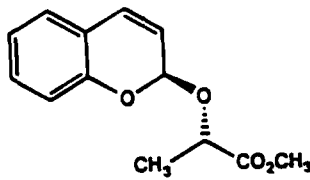
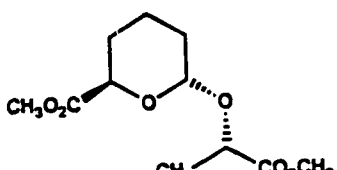
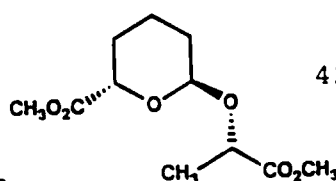
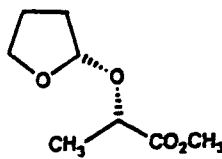
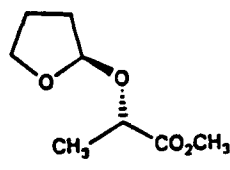
^aIsolated yields of the less polar (a) and more polar (b) diastereomers, respectively. ^bThe separation factor, α , is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). ^cSolvent is given as the percent ethyl acetate used in hexanes.

Table 1 (cont). Separation of Diastereomeric THP
and THF Ethers of α -Hydroxy Esters

Entry	Diastereomeric Acetals	Yields ^a , %	α^b (Solvent) ^c	
7	 <u>13a</u>	 <u>13b</u>	33,42	1.18 (20)
8	 <u>14a</u>	 <u>14b</u>	49,47	1.40 (20)
9	 <u>15a</u>	 <u>15b</u>	42,42	1.30 (20)
10	 <u>16a</u>	 <u>16b</u>	31,38	1.34 (20)

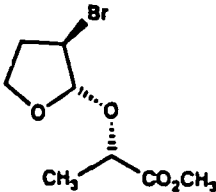
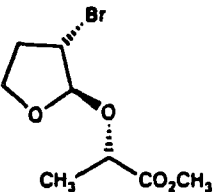
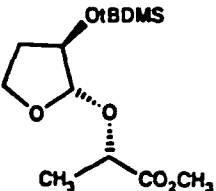
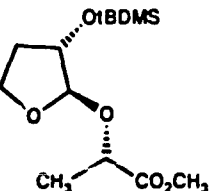
^aIsolated yields of the less polar (a) and more polar (b) diastereomers, respectively. ^bThe separation factor, α , is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). ^cSolvent is given as the percent ethyl acetate used in hexanes.

Table 1 (cont). Separation of Diastereomeric THP
and THF Ethers of α -Hydroxy Esters

<u>Entry</u>	<u>Diastereomeric Acetals</u>	<u>Yields^a, %</u>	<u>α^b(Solvent)^c</u>	
11	 <u>17a</u>	 <u>17b</u>	48, 23	1.22 (10)
12	 <u>18a</u>	 <u>18b</u>	41, 17	1.58 (5)
13	 <u>19a</u>	 <u>19b</u>	42, 40	1.09 (50)
14	 <u>20a</u>	 <u>20b</u>	45, 48	1.25 (20)

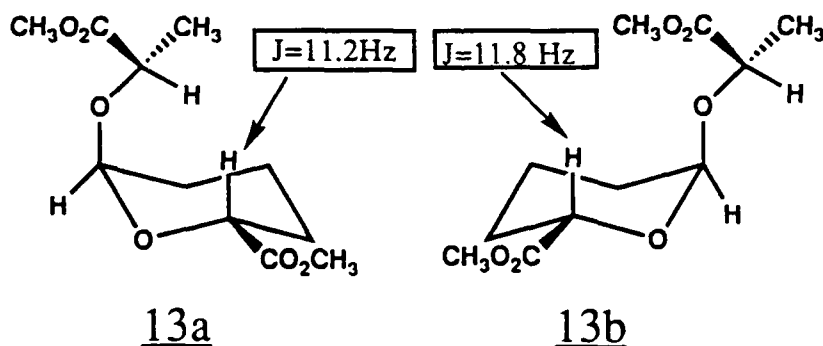
^aIsolated yields of the less polar (a) and more polar (b) diastereomers, respectively. ^bThe separation factor, α , is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). ^cSolvent is given as the percent ethyl acetate used in hexanes.

Table 1 (cont). Separation of Diastereomeric THP
and THF Ethers of α -Hydroxy Esters

<u>Entry</u>	<u>Diastereomeric Acetals</u>	<u>Yields^a, %</u>	<u>α^b(Solvent)^c</u>	
15	 <u>21a</u>	 <u>21b</u>	43, 44	1.10 (20)
16	 <u>22a</u>	 <u>22b</u>	36, 36	1.19 (20)

^aIsolated yields of the less polar (a) and more polar (b) diastereomers, respectively. ^bThe separation factor, α , is the ratio of R_f values for diastereomers a and b on 0.25 mm silica gel 60 plates (Merck, 70-230 mesh). ^cSolvent is given as the percent ethyl acetate used in hexanes.

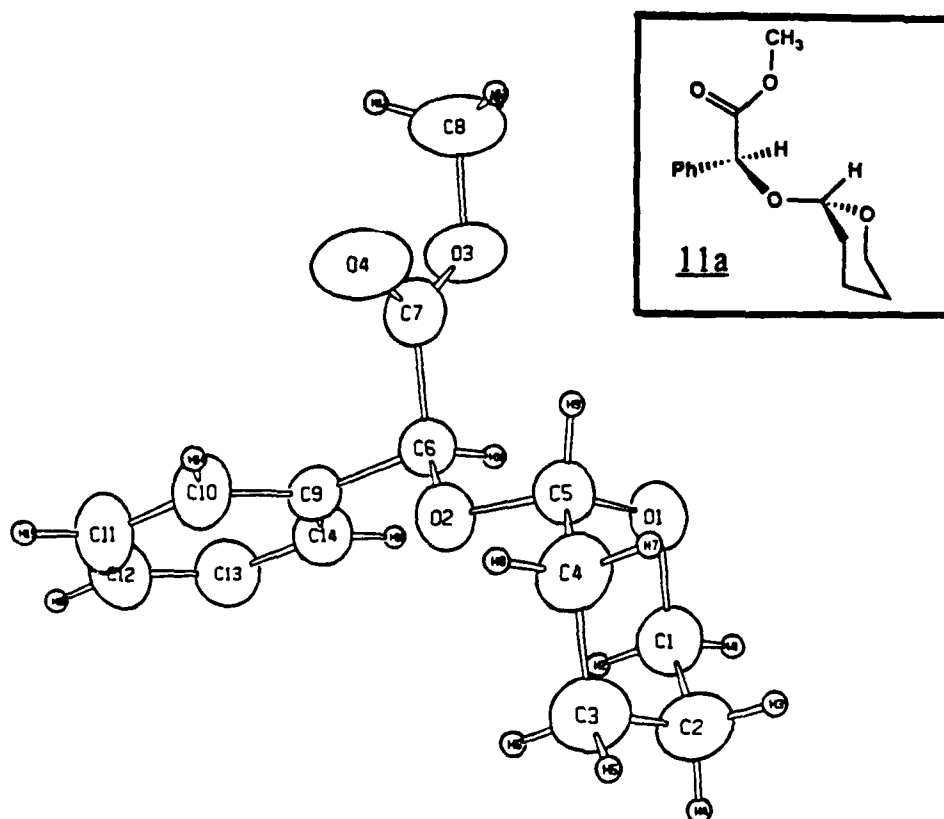
It is important to stress that the only difference between these diastereomers is the chirality of the newly formed anomeric center on the ring portion of the molecule. It is also important to note that in entries 9, 13, 15, and 16 there is a second stereogenic center on the ring which is stereochemically linked to the chirality of the anomeric center. For example, for both diastereomers of entry 13 the carbomethoxy substituent adopts the equatorial orientation and the lactate adopts the axial conformation as shown by the ^1H NMR coupling constants (Scheme 4). This stereochemical link is an encouraging sign that the chirality of the anomeric center may be able to direct the steric course of subsequent reactions performed on the ring.



SCHEME 4: NMR EVIDENCE OF STEREOCHEMICAL LINKING

In order to be able to predict the steric course of these later reactions we needed to know the absolute stereochemistry for each of the resolved diastereomers. We determined the absolute stereochemistry by two methods. First, the less

polar diastereomer of the (S)-methyl mandelate pyranosides (Entry 5) was sufficiently crystalline so that a crystal structure could be obtained (the data are tabulated in Appendix A). The crystal structure showed that the less polar diastereomer of the (S)-methyl mandelate pyranosides has the (S)-stereochemistry at the anomeric center (an ORTEP plot is shown in Scheme 5). Prior studies¹⁻⁹ of crystalline THP derivatives had demonstrated that the diastereomers with the

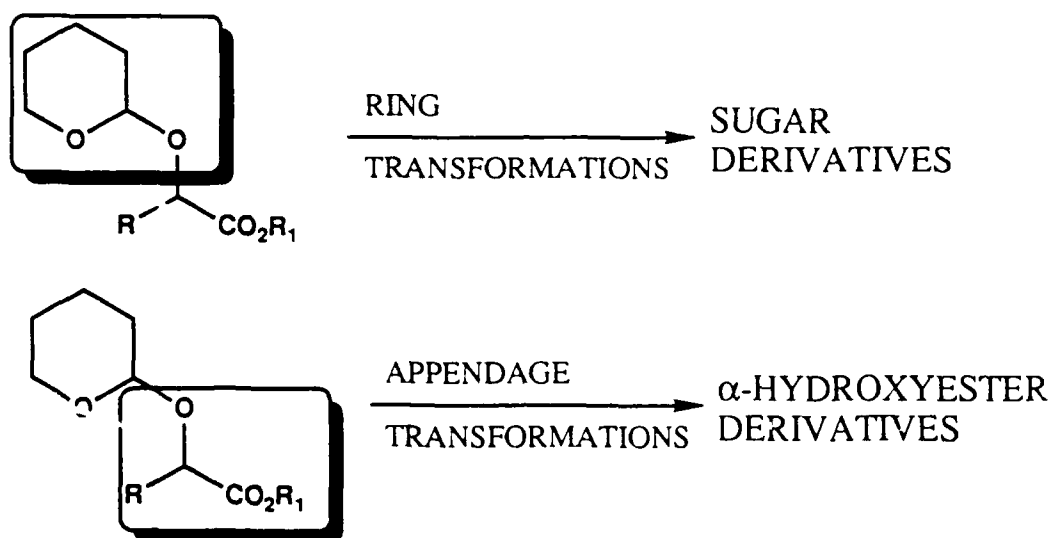


SCHEME 5: ORTEP PLOT OF THE LESS POLAR (S)-METHYL MANDELYL THP ETHER

(S)-stereochemistry at the anomeric center also were the more levorotatory--this was also found to be the case for the mandelate THP as well (less polar diastereomer $[\alpha]_D^{21} -45.17^\circ$, more polar diastereomer $[\alpha]_D^{20} +169.3^\circ$). Our second determination of absolute stereochemistry was done by conversion of 2 resolved pyranosides to natural products. In work performed by Jeff Arterburn¹⁰⁻¹¹ the pyranoside 16a was converted to the known (2S,3R) 1,2,3,5-tetra-O-benzoyl erythro pentitol (thus confirming the (S)-stereochemistry of 16a) while a similar reaction sequence with 16b afforded the (2R,3S) pentitol (thus confirming the (R)-stereochemistry of 16b). Catalytic hydrogenation of 16a afforded 7a while hydrogenation of 16b afforded 7b. This indicates that 7a also has (S)-stereochemistry while 7b has (R)-stereochemistry. The other pyranosides and furanosides were assumed to have corresponding stereochemistry.

Once the separation of the diastereomers is completed two possibilities exist for attempting diastereoselective reactions. As shown in Scheme 6, the first possibility is to perform diastereoselective reactions on the ring portion of the molecule--the result of such reactions could lead to sugar derivatives. Work in this area was performed by Jeff Arterburn and has been published¹⁰⁻¹³. The second possibility is to perform diastereoselective reactions on the α -hydroxy ester portion of the molecule. Research in that area is

discussed in Chapter 2.



SCHEME 6: POSSIBLE DIASTEREOSELECTIVE REACTIONS ON THP ETHERS

EXPERIMENTAL:

Diethyl ether, benzene, and THF were distilled from sodium benzophenone ketyl under an inert atmosphere. PPTS was recrystallized from hexanes. Proton magnetic resonance spectra were recorded at 250 MHz on a Bruker WM-250 NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) from tetramethylsilane. Carbon-13 magnetic resonance spectra were recorded at 62.9 MHz on a Bruker WM-250 spectrometer; chemical shifts are reported as δ values in ppm from the center line of the chloroform-d triplet (77.0 ppm). In NMR data for mixed diastereomers signals belonging to the major diastereomer are underlined. Mass spectral determinations were performed at the Midwest Center for Mass Spectrometry at the University of Nebraska. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70-230 mesh ASTM). Column chromatography was performed using Merck silica gel 60 (gravity driven, 70-230 mesh ASTM; flash, 230-400 mesh ASTM). Melting points were determined on a Thomas Hoover Unimelt Capillary Melting Point Apparatus and are uncorrected.

(S)-Methyl Lactyl Tetrahydropyranyl Ethers (7a and 7b).

To a well-stirred solution of dihydropyran (2 mL, 1.84g,

22 mmol) in dry CH_2Cl_2 (5 mL) were added (S)-methyl lactate (1.0 mL, 1.09g, 10.5 mmol) and pyridinium p-toluenesulfonate (PPTS, 50 mg, 0.2 mmol). After 16 hours at room temperature, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated NaHCO_3 (25 mL), then dried (Na_2SO_4), filtered, and volatiles removed in vacuo. The residue was chromatographed twice on silica gel 60 (200g) eluted with 15% ethyl acetate/hexanes, affording 970 mg (5.16 mmol, 49%) each of 7a and 7b. Spectral data for 7a (R_f 0.317, 20% EtOAc/hexanes): $[\alpha]_D^{24} -144^\circ$ (c 3.04, EtOAc); IR (neat) 2944, 1751 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.45 (3,d, $J=6.9$ Hz), 1.40-2.90 (6,m), 3.45-3.54 (1,m), 3.74 (3,s), 3.75-3.90 (1,m), 4.43 (1,q, $J=6.9$ Hz), 4.70 (1,m, $J<4$ Hz); ^{13}C NMR (CDCl_3) δ 18.54 (CH_3), 18.90 (CH_2), 25.13 (CH_2), 30.12 (CH_2), 51.62 (CH_3), 62.15 (CH_2), 69.65 (CH), 97.31 (CH), 173.54 (C).

For 7b (R_f 0.267): $[\alpha]_D^{24} +70.1^\circ$ (c 3.90, EtOAc); ^1H NMR (CDCl_3) δ 1.40 (3,d, $J=6.7$ Hz), 1.50-1.95 (6,m), 3.40-3.50 (1,m), 3.74 (3,s), 3.85-4.00 (1,m), 4.22 (1,q, $J=6.7$ Hz), 4.71 (1,m, $J<4$ Hz); ^{13}C NMR (CDCl_3) δ 17.87 (CH_3), 19.04 (CH_2), 25.10 (CH_2), 30.30 (CH_2), 51.75 (CH_3), 62.27 (CH_2), 72.24 (CH), 98.17 (CH), 173.55 (C); mass spectrum (70 eV) m/z (rel. intensity) 187 (0.4), 133 (2), 130 (3), 129 (3), 101 (16), 86 (7), and 85 (100); exact mass calc. for $\text{C}_9\text{H}_{15}\text{O}_4$ (M^+-H^+) 187.0970, obsd. 187.0975.

(S)-Ethyl Lactyl Tetrahydropyranyl Ethers (8a and 8b).

These diastereomers were similarly prepared and separated. Spectral data for 8a (R_f 0.333, 20% EtOAc/hexanes): $[\alpha]_D^{25}$ -151.2° (c 6.33, $CHCl_3$); IR ($CHCl_3$) 2942, 1729, 1209, 1125, 1020 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.28 (3,t, $J=7.1$ Hz), 1.45 (3,d, $J=7.0$ Hz), 1.50-1.88 (6,m), 3.49-3.56 (1,m), 3.80-3.89 (1,m), 4.13-4.24 (2,m), 4.41 (1,q, $J=7$ Hz), 4.70 (1,t, $J=3.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.86 (CH_3), 18.39 (CH_3), 18.80 (CH_2), 25.07 (CH_2), 30.01 (CH_2), 60.39 (CH_2), 61.97 (CH_2), 69.53 (CH), 97.11 (CH), 172.92 (C).

For 8b (R_f 0.283): $[\alpha]_D^{26}$ $+45.64^\circ$ (c 6.59, $CHCl_3$); IR ($CHCl_3$) 2939, 1729, 1124, 1036 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.29 (3,t, $J=7.1$ Hz), 1.40 (3,d, $J=6.9$ Hz), 1.44-1.73 (6,m), 3.43-3.52 (1,m), 3.88-3.99 (1,m), 4.14-4.24 (3,m), 4.72 (1,t, $J=3.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 17.8 (CH_3), 18.9 (CH_2), 25.1 (CH_2), 30.2 (CH_2), 60.4 (CH_2), 62.0 (CH_2), 72.3 (CH), 98.1 (CH), 173.0 (C).

(S)-Isopropyl Lactyl Tetrahydropyranyl Ethers (9a and 9b).

These diastereomers were similarly prepared and separated. Spectral data for 9a (R_f 0.362, 20% EtOAc/hexanes): $[\alpha]_D^{24}$ -135.2° (c 5.0, $CHCl_3$); IR ($CHCl_3$) 2943, 1736, 1374, 1224, 1200, 1127, 1101, 1033, 1021 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.23-1.27 (6,m), 1.43 (3,d, $J=7$ Hz), 1.51-1.88 (6,m), 3.49-3.55 (1,m), 3.80-3.88 (1,m), 4.38 (1,q, $J=7$ Hz), 4.69

(1,t,J=3 Hz), 5.06 (1,m,J=6 Hz); ^{13}C NMR (CDCl_3) δ 18.53 (CH_3), 19.00 (CH_2), 21.62 (2CH_3), 25.24 (CH_2), 30.22 (CH_2), 62.22 (CH_2), 68.11 (CH), 69.84 (CH), 97.33 (CH), 172.75 (C).

For 9b (R_f 0.319): $[\alpha]_D^{25} +48.54^\circ$ (c 5.0, CHCl_3); IR (CHCl_3) 2980, 1728, 1452, 1373, 1285 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.258 (3,d,J=6.2 Hz), 1.264 (3,d,J=6.2 Hz), 1.382 (3,d,J=6.8 Hz), 1.51-1.88 (6,m), 3.41-3.49 (1,m), 3.89-3.96 (1,m), 4.131 (1,q,J=6.8 Hz), 4.719 (1,t,J=3.2 Hz), 5.055 (1,m,J=6.2 Hz); ^{13}C NMR (CDCl_3) δ 17.92 (CH_3), 18.93 (CH_2), 21.51 (2CH_3), 25.16 (CH_2), 30.29 (CH_2), 62.04 (CH_2), 67.85 (CH), 72.53 (CH), 98.15 (CH), 172.67 (C).

(S)-t-Butyl Lactyl Tetrahydropyranyl Ethers (10a/b).

To a well-stirred solution of dihydropyran (0.797g, 9.5 mmol) in dry CH_2Cl_2 (3 mL) were added (S)-t-butyl lactate (327.2 mg, 2.24 mmol) and PPTS (ca. 5 mg, 0.02 mmol). After 80 minutes at room temperature, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated NaHCO_3 (5 mL), then dried (MgSO_4), filtered, and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (50g) eluted with 5% ethyl acetate/hexanes, affording 384.8 mg (74.65%) of the mixed diastereomers (R_f less polar 0.469, more polar 0.375; 20% EtOAc/hexanes) as a colorless oil. Spectral data for the mixture: IR (CHCl_3) 3007, 2943, 2871, 1729, 1453, 1392, 1368, 1352, 1305, 1232, 1127, 1100, 1075, 1055, 1034, 986, 942, 903,

872, 846, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.3566 (3,d,J=6.8 Hz) and 1.4172 (3,d,J=7.0 Hz), 1.4694 and 1.4739 (9,s), 1.40-1.95 (6,m), 3.41-3.57 (1,m), 3.80-4.00 (1,m), 4.0539 (1,q,J=6.8 Hz) and 4.2981 (1,q,J=7.0 Hz), 4.69-4.73 (1,m).

(S)-Methyl Mandelyl Tetrahydropyranyl Ethers (11a and 11b).

These diastereomers were similarly prepared and separated. Spectral data for 11a (mp 49.8-52.7°C, R_f 0.360, 20% EtOAc/hexanes): $[\alpha]_D^{21}$ -45.17° (\underline{c} 4.10, CHCl_3); IR (CHCl_3) 3015, 2946, 1744, 1453, 1261, 1212, 1122, 1067, 1035 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.45-1.90 (6,m), 3.47-3.53 (1,m), 3.71 (3,s), 3.65-3.75 (1,m), 4.89 (1,t,J=2.5 Hz), 5.33 (1,s), 7.26-7.51 (5,m); ^{13}C NMR (CDCl_3) δ 18.60 (CH_2), 25.26 (CH_2), 30.10 (CH_2), 52.18 (CH_3), 61.85 (CH_2), 75.50 (CH), 97.05 (CH), 127.16 (CH), 128.35 (CH), 128.47 (CH), 136.70 (C), 171.81 (C).

For 11b (R_f 0.326): $[\alpha]_D^{20}$ +169.3° (\underline{c} 2.83, CHCl_3); IR (CHCl_3) 3026, 3011, 2949, 1742, 1453, 1435, 1260, 1208, 1202, 1122, 1079, 1035 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.50-2.00 (6,m), 3.45-3.55 (1,m), 3.704 (3,s), 3.90-4.00 (1,m), 4.58 (1,t,J=3.5 Hz), 5.245 (1,s), 7.26-7.48 (5,m); ^{13}C NMR (CDCl_3) δ 18.98 (CH_2), 25.21 (CH_2), 30.16 (CH_2), 52.15 (CH_3), 62.35 (CH_2), 76.65 (CH), 96.47 (CH), 127.43 (CH), 128.53 (CH), 136.20 (C), 171.10 (C).

(S)-Methyl Lactyl 6-Carbomethoxytetrahydropyranyl Ethers (19a and 19b).

These diastereomers were similarly prepared and separated. Spectral data for 19a (R_f 0.459, 50% EtOAc/hexanes): $[\alpha]_D^{19}$ -111.6° (≤ 5.0 , CHCl_3); IR (CHCl_3) 2953, 1750, 1441, 1371, 1040 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.45 (3,d,J=7 Hz), 1.55-2.04 (6,m), 3.73 (3,s), 3.77 (3,s), 4.39 (1,dd, J=2.1, 11.2 Hz), 4.44 (1,q,J=7 Hz), 5.05 (1,bs); ^{13}C NMR (CDCl_3) δ 17.22 (CH_2), 18.51 (CH_3), 27.97 (CH_2), 28.65 (CH_2), 51.69 (CH_3), 51.89 (CH_3), 68.68 (CH), 69.73 (CH), 96.34 (C), 171.92 (C), 173.19 (C).

For 19b (R_f 0.422): $[\alpha]_D^{20}$ $+25.88^\circ$ (≤ 5.0 , CHCl_3); IR (CHCl_3) 2956, 1750, 1441, 1370, 1040 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.40 (3,d,J=7 Hz), 1.25-2.08 (6,m), 3.75 (3,s), 3.76 (3,s), 4.22 (1,q,J=7 Hz), 4.61 (1,bd,J=11.8 Hz), 5.05 (1,bs); ^{13}C NMR (CDCl_3) δ 17.50 (CH_2), 17.85 (CH_3), 27.77 (CH_2), 28.93 (CH_2), 51.69 (2 CH_3), 68.54 (CH), 72.80 (CH), 97.62 (CH), 171.98 (C), 173.32 (C).

Methyl 3-Hydroxyfuranoside.

Dihydrofuran (6.040g, 86.17 mmol) was dissolved in CH_3OH (80 mL) and cooled in an ice bath. Magnesium monoperoxyphthalic acid (26.558g, 43 mmol) was added portionwise with stirring over 20 minutes and the reaction was warmed to room temperature. The reaction mixture was stirred for 48 hours and diluted with 500 mL ether; the slurry was filtered and the solid rinsed with an additional 100 mL ether. The combined

ether layers were washed with sat NaHCO_3 (50 mL) and the aqueous phase extracted with 3 x 50 mL ether. The combined ether phases were dried (MgSO_4), filtered, and distilled to give 4.82g (47%) of the alcohol as a colorless oil (b.p. 110°C , 18 torr). ^1H NMR (CDCl_3) δ 1.78-1.90 (1,m), 2.19-2.34 (1,m), 2.52 (1,s), 3.34 (3,s), 3.90-4.00 (1,m), 4.07-4.17 (1,dd,J=8 Hz), 4.22 (1,dd,J=1.6 Hz, 5.5 Hz), 4.82 (1,s).

Methyl 3-t-Butyldimethylsilyloxytetrahydrofuranoside.

To a stirred solution of methyl 2-hydroxyfuranoside (1.565g, 13.25 mmol) and imidazole (2.02g, 29.7 mmol) in 15 mL DMF at 0°C was added a solution of t-butyldimethylsilyl chloride (2.2275g, 14.78 mmol) in 5 mL DMF. The reaction was allowed to warm to room temperature and stirred overnight. The solution was then diluted with 150 mL of diethyl ether and washed with three 15 mL portions of water. The ether solution was dried with MgSO_4 , filtered, and the solvent removed in vacuo. The concentrate was chromatographed on silica gel 60 (200g) eluted with 5% EtOAc/hexanes to afford 1.9122g (62.11%) of the silyl ether as a colorless oil. Spectral data (R_f 0.53, 20% EtOAc/hexanes): IR (CHCl_3) 2954, 1470, 1462, 1256, 1124, 1102, 1046, 838 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.083 (6,s), 0.890 (9,s), 1.69-1.81 (1,m), 2.08-2.21 (1,m), 3.321 (3,s), 3.89-3.98 (1,m), 4.075 (1,q,J=7.7 Hz), 4.187 (1,dd,J=1.9, 5.4 Hz), 4.724 (1,s); ^{13}C NMR (CDCl_3) δ -4.885 (CH_3), 18.039 (C), 25.738

(CH₃), 33.154 (CH₂), 54.359 (CH₃), 66.737 (CH₂), 76.354 (CH), 109.591 (CH).

(S)-Methyl Lactyl 2-O-t-Butyldimethylsilyl-2-hydroxyfuranosides (22a and 22b).

A stirred solution of methyl 2-O-t-butyldimethylsilyl-2-hydroxyfuranoside (0.8028g, 3.454 mmol), (S)-methyl lactate (0.8070g, 7.752 mmol), and tosic acid (50 mg) in 20 mL benzene was heated to reflux and the benzene/methanol azeotrope removed via a Dean-Stark trap. After six hours and removal of 120 mL of collected azeotrope, the reaction mixture was cooled to room temperature, diluted with 100 mL diethyl ether, washed with 10 mL saturated NaHCO₃, dried with MgSO₄, filtered and volatiles removed in vacuo. The concentrate was separated on 70g of flash silica eluted with 5% EtOAc/hexanes to afford recovered starting material (93.9 mg) and 368 mg (1.21 mmol, 36%) each of 22a and 22b. Spectral data for 22a (R_f 0.44, 20% EtOAc/hexanes): $[\alpha]_D^{23}$ -99.12° (c 2.85, CHCl₃); IR (CHCl₃) 2951, 1743, 1122 cm⁻¹; ¹H NMR (CDCl₃) δ 0.099 (6,s), 0.890 (9,s), 1.371 (3,d,J=7 Hz), 1.72-1.84 (1,m), 2.12-2.28 (1,m), 3.738 (3,s), 3.90-3.99 (1,m), 4.092 (1,q,J=7.8 Hz), 4.307 (1,dd, J=1.5, 5.2 Hz), 4.346 (1,q,J=7 Hz), 4.944 (1,s); ¹³C NMR (CDCl₃) δ -4.98 (CH₃), -4.90 (CH₃), 18.00 (C), 18.80 (CH₃), 25.71 (CH₃), 32.83 (CH₂), 51.81 (CH₃), 67.08 (CH₂), 69.61 (CH), 76.27 (CH), 107.05 (CH), 173.43 (C).

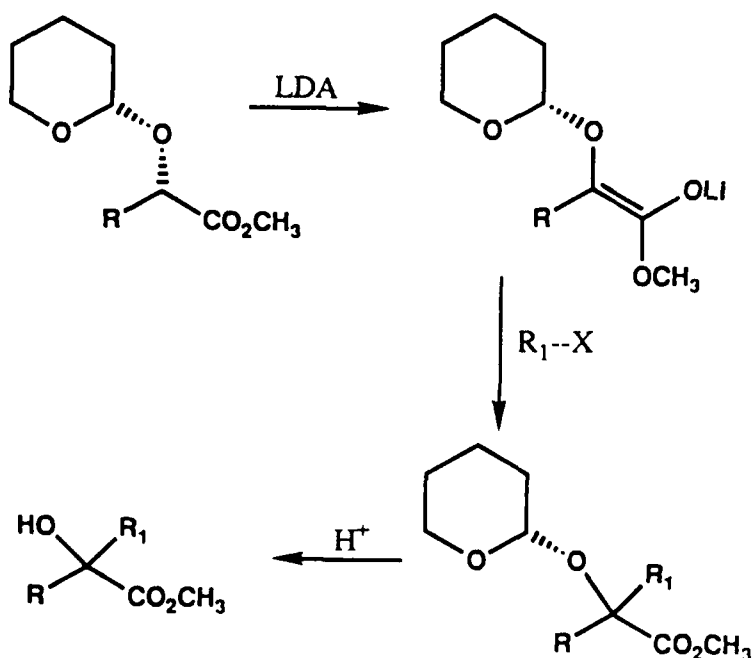
For 22b (R_f 0.37): $[\alpha]_D^{23} +21.28^\circ$ (c 4.14, CHCl_3); IR (CHCl_3) 2953, 1745, 1126 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.078 (6,s), 0.880 (9,s), 1.368 (3,d, $J=6.9$ Hz), 1.70-1.85 (1,m), 2.20-2.35 (1,m), 3.72 (3,s), 3.86-3.96 (1,m), 4.02 (1,q, $J=7.7$ Hz), 4.09 (1,q, $J=6.8$ Hz), 4.29 (1,dd, $J=1.9, 5.3$ Hz), 4.91 (1,s); ^{13}C NMR (CDCl_3) δ -4.88 (CH_3), 17.98 (C), 18.18 (CH_3), 25.69 (CH_3), 33.15 (CH_2), 51.77 (CH_3), 67.41 (CH_2), 71.44 (CH), 76.44 (CH), 108.23 (CH), 174.00 (C); mass spectrum (70 eV) m/z (rel. intensity) 247 (1), 233 (3), 203 (4), 202 (6), 201 (45), 185 (1), 175 (4), 172 (4), 171 (2), 162 (7), 161 (59), 145 (7), 133 (6), 129 (6), 116 (10), 115 (100), 101 (12), 89 (20), 75 (23), 73 (48), 59 (11); high resolution calcd. for $\text{C}_{10}\text{H}_{19}\text{O}_5\text{Si}$ (M^+-tBu) 247.1002, obsd. 247.0997.

Correlation of the Absolute Stereochemistry of the Lactate Pyranosides 16a and 7a.

Approximately 15 mg of the 2S,2'S methyl lactyl 5,6-dihydropyranyl acetal 16a (which had been converted to (2S,3R)-1,2,3,5-tetra-O-benzoyl-erythro-pentitol thus confirming the 2S stereochemistry^{10,11}) was dissolved in 1 mL of dry EtOAc and 25 mg of 5% rhodium on carbon was added. The solution was stirred under a hydrogen atmosphere for 2 hours. TLC showed formation of the less polar diastereomer of the tetrahydropyranoside (7a) thus confirming the 2S stereochemistry for that diastereomer.

CHAPTER 2. ALKYLATION OF LITHIUM ENOLATES DERIVED FROM α -HYDROXY ESTER TETRAHYDROFURANYL AND TETRAHYDROPYRANYL ETHERS.

With the separated pyranosides of a variety of α -hydroxy esters in hand the next step was to investigate the utility of these now-chiral auxiliaries for directing the steric course of reactions. In examining the structures of the pyranosides the ester function on the appendage offered the possibility of being a handle on which to perform some interesting chemistry. We decided to first investigate the possibility for alkylations. As shown in Scheme 7, treatment of the ester with LDA or other bases would generate the enolate which could

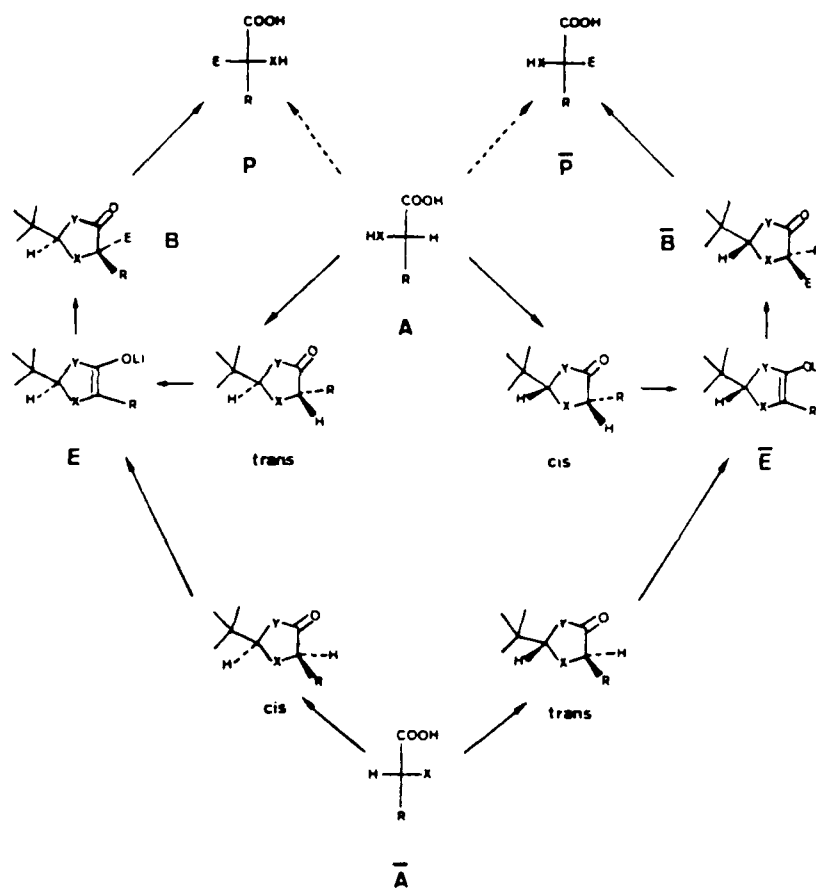


SCHEME 7: ALKYLATIONS OF α -HYDROXYESTER THP ETHERS

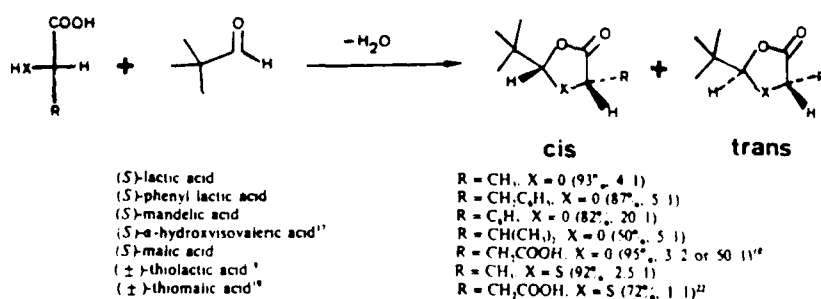
then be reacted with electrophiles. The result of alkylations on the enolate would be α -alkyl α -hydroxy esters which could be useful building blocks for the synthesis of natural products. Before embarking down this pathway, however, it seems prudent to review some of the literature methods for making such esters.

A. METHODS FOR DIASTEREOSELECTIVE ALKYLATION OF α -HYDROXY CARBONYLS.

The work that most closely resembles the alkylation reactions we sought to examine was done by Dieter Seebach¹⁴ (Scheme 8). In this method, an α -hydroxyacid is condensed with pivaldehyde to form a 2-t-butyl-5-substituted-1,3-dioxolanone. The yields varied from 50-95% and the cis:trans ratio varied from 1:1 to 50:1 depending on the α -hydroxyacid and the solvent. In all but one case, the diastereomers could be purified by recrystallization. The dioxolanone (either cis or trans) was then treated with lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) to form the lithium enolate which could be alkylated using alkyl halides or could be condensed with aldehydes or ketones. In the case of the alkylations the yields ranged from 30-92% and the diastereoselectivities were all greater than 95%. In many cases none of the product resulting from alkylation on the face cis to the t-butyl group was observed. A drawback to this method,



α -Alkylation of an acid A to a product P with self-reproduction of chirality



SCHEME 8: SEEBACH'S METHOD FOR "SELF-REPRODUCTION OF CHIRALITY"

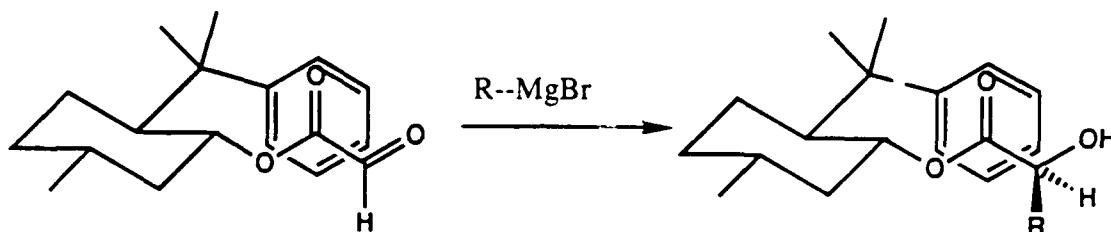
however, is the fact that given a starting chirality for the α -hydroxyacid the steric course for the major product is

fixed--one cannot easily obtain the other diastereomer without recycling. For example, (S)-lactic acid gives a 4:1 ratio of the cis:trans dioxolanones and the cis isomer is alkylated on the Si face to give the alkylated product with the (R) configuration. If one wanted the product with the (S) configuration he would either have to start with (R)-lactic acid (which would be more expensive) or would have to alkylate the trans isomer and recycle the cis (which would not be efficient use of time and resources).

Seebach's α -alkylation with "self-reproduction of chirality" is similar to the method we have developed here in that he uses an acetal to direct the alkylation on an enolate. However, the driving force for the diastereoselectivity in the alkylation on the dioxolanones is the effective steric hindrance by the t-butyl group to block one face of the enolate. For the tetrahydropyranyl ethers in our method steric blocking will be much less of a factor but coordination of the lithium enolate to the pyran oxygen should predominate.

A second method of producing α -hydroxy esters diastereoselectively using an 8-phenylmenthol chiral auxiliary (developed by Corey¹⁵) has been investigated by Whitesell and by Pearson. Whitesell¹⁶ was the first to prepare the 8-phenylmenthyl ester of glyoxalic acid (glycolic acid aldehyde) and to perform diastereoselective alkylations on the molecule. Using alkyl Grignard reagents (as shown in Scheme 9) he was

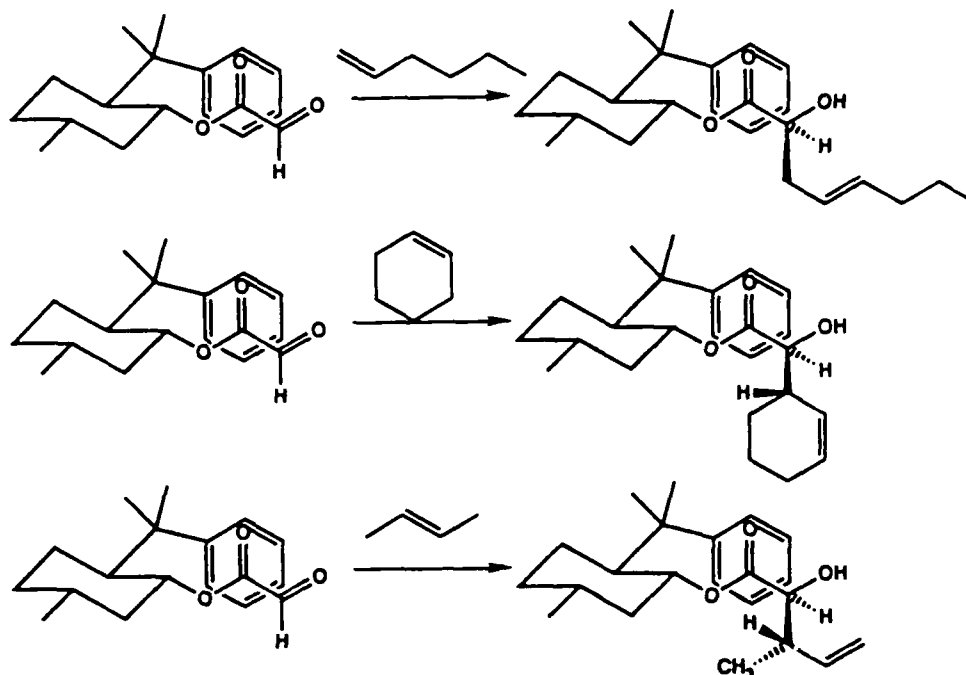
able to selectively alkylate the Si face of the aldehyde with d.e.'s greater than 98% and in yields ranging from 80-90%. Alkylolithium or alkylzinc reagents could also be used in the alkylations but the diastereoselectivity was considerably



SCHEME 9: WHITESELL'S METHOD USING GRIGNARD REAGENTS

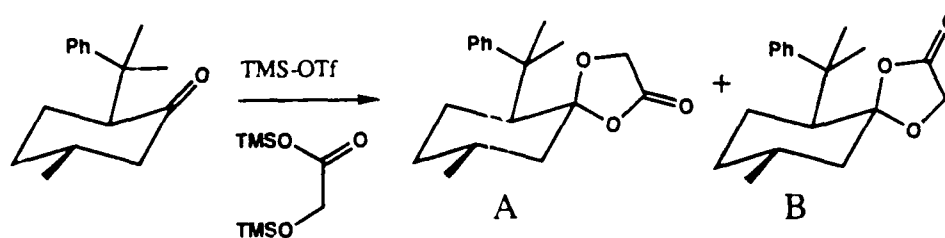
lower (20-60% d.e.'s). Whitesell was also able to perform ene reactions on the molecule¹⁷ (Scheme 10) using tin tetrachloride as catalyst which again showed high diastereoselectivity (93-97.6% d.e.) and proceeded in good to excellent yields (75-92%). Through a subsequent study¹⁸ he was able to demonstrate that the diastereoselectivity of the reaction was very dependent on the structure of the chiral auxiliary and especially on the presence of an aromatic ring close to the glyoxylate.

Another method beginning with 8-phenylmenthol was developed by Pearson¹⁹. Pearson first oxidized 8-phenylmenthol to the ketone and then reacted it with trimethylsilyl (trimethylsilyloxy)acetate with catalytic trimethylsilyl trifluoromethanesulfonate (TMS-OTf) to form the chiral 1,3-



SCHEME 10: WHITESELL'S METHOD USING ENE REACTIONS

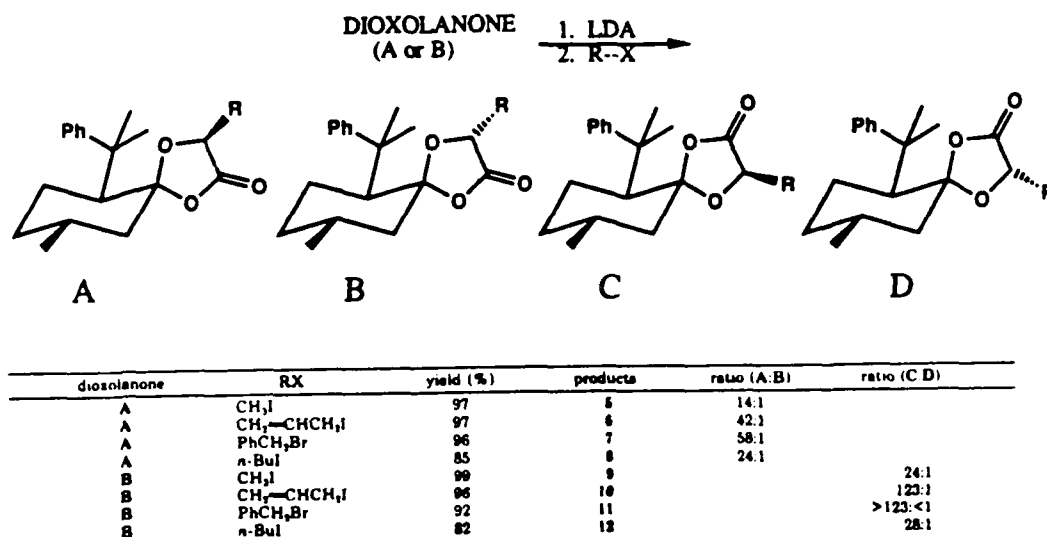
dioxolan-4-ones²⁰ in approximately equal amounts (Scheme 11).



SCHEME 11: PEARSON'S SYNTHESIS OF CHIRAL 1,3-DIOXOLAN-4-ONES

The glycolate esters were then separated by flash chromatography and were treated with LDA followed by an alkyl halide to afford the alkylated products in 82-99% yield with

diastereoselectivities ranging from 14:1 to >123:1 (Scheme 12). These product diastereomers could also be purified by flash chromatography. The chiral auxiliary was then removed using refluxing ethanolic HCl to give the enantiomerically pure alkylated product in 83-95% yield. The auxiliary was



SCHEME 12: ALKYLATIONS OF PEARSON'S DIOXOLANONES

also recovered in 95-99% yield with no loss of optical activity. An important aspect of this method is that both alkylated products are equally available by choosing which of the dioxolanones is alkylated.

Pearson was also able to perform diastereoselective aldol condensations on the chiral glycolate enolates and was thus able to obtain α,β -dihydroxy esters in optically pure form²¹. As shown in Scheme 13, treatment of the chiral glycolate esters with LDA followed by addition of a metal salt and an

aldehyde gave the aldol condensation products in 85-99% yield. The facial selectivity was 100% for the face of the glycolate away from the appendage on the menthone and the syn/anti selectivity could be controlled by the selection of the added metal ion. Resolution of the product diastereomers followed by hydrolysis with ethanolic HCl afforded the optically pure compounds.

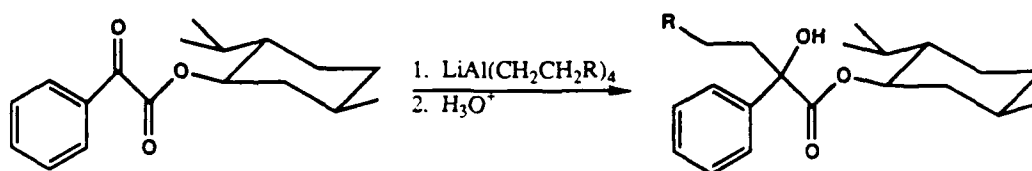
diosolanone	M ⁺	RCHO	yield (%) ^d	ratio	
				3:4	5:6
1	Li ⁺	PhCHO	92	2:1:0	
1	Mg ²⁺	PhCHO	92	4:8:0	
1	Zr ⁴⁺	PhCHO	95	10:4:3	
1	Li ⁺	n-PrCHO	93	25:3:0	
1	Mg ²⁺	n-PrCHO	86	9:3:0	
1	Zr ⁴⁺	n-PrCHO	97	10:1:2	
1	Li ⁺	i-PrCHO	85	9:4:0	
1	Mg ²⁺	i-PrCHO	86	2:7:0	
1	Zr ⁴⁺	i-PrCHO	91	10:3:1	
2	Li ⁺	PhCHO	99		2:1:0
2	Mg ²⁺	PhCHO	89		3:0:0
2	Zr ⁴⁺	PhCHO	91		10:4:7
2	Li ⁺	n-PrCHO	96		7:0:0
2	Mg ²⁺	n-PrCHO	92		2:9:0
2	Zr ⁴⁺	n-PrCHO	91		1:0:1
2	Li ⁺	i-PrCHO	86		26:2:0
2	Mg ²⁺	i-PrCHO	89		8:0:0
2	Zr ⁴⁺	i-PrCHO	89		10:5:0

^a All reactions were carried out in THF (ca. 0.1 M) at -78 °C. ^b a, R = Ph; b, R = n-C₃H₇; c, R = i-C₃H₇. ^c For M⁺ = Li⁺, no extra metal added. For M⁺ = Mg²⁺, MgBr₂ (1 equiv) was added. For M⁺ = Zr⁴⁺, Cp₂ZrCl₂ (1 equiv) was added. ^d Isolated, purified yields.

SCHEME 13: PEARSON'S METHOD USING ALDOL CONDENSATION

Another method of alkylating menthol glycolate esters was

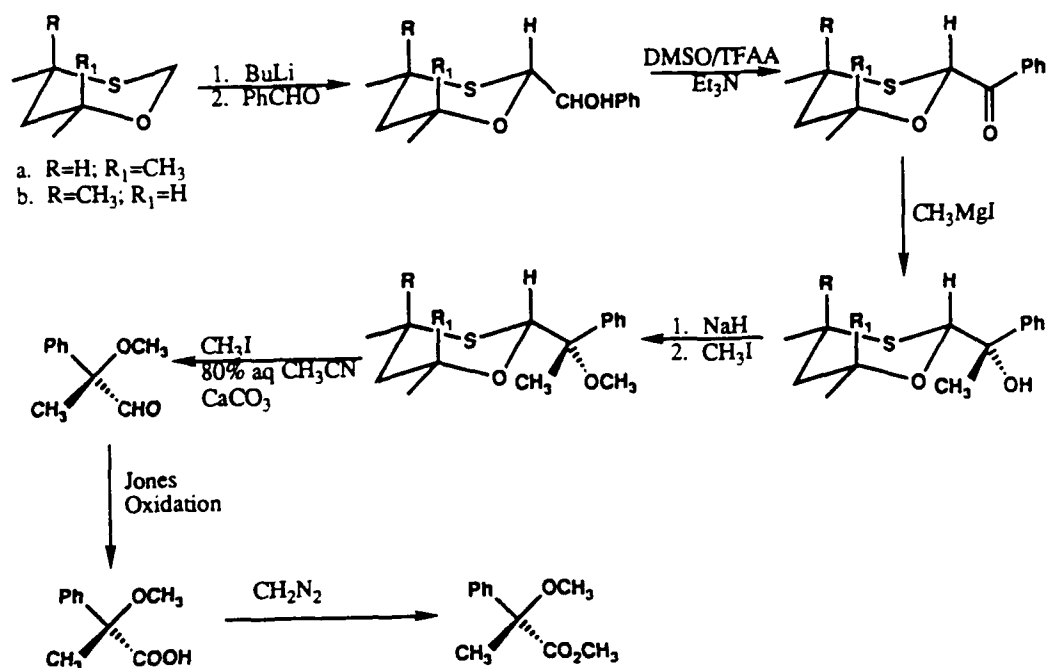
developed by Boireau²². Alkylation of the (-)-menthyl ester of phenylglyoxylic acid with a variety of tetraalkylaluminates (Scheme 14) gave the diastereoselectively alkylated products in 58-80% yield with d.e.'s from 64-76%.



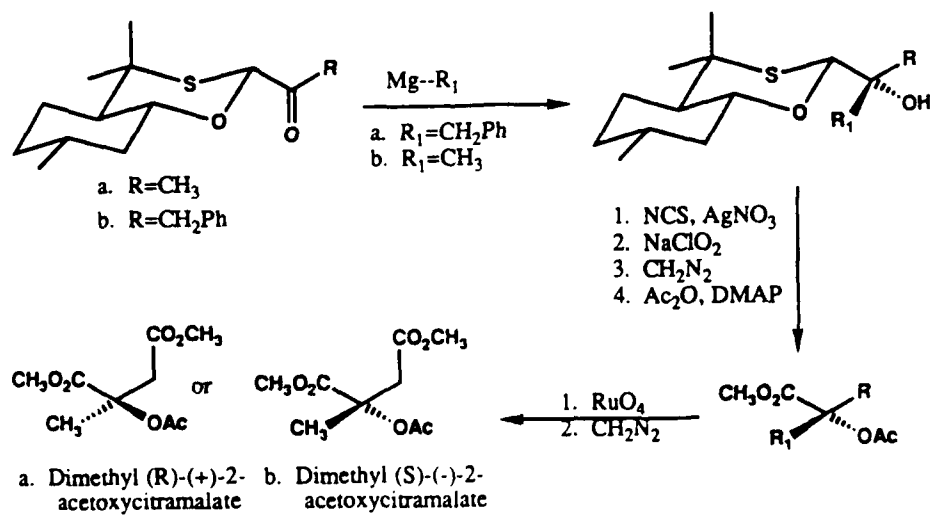
SCHEME 14: BOIREAU'S METHOD USING TETRAALKYLALUMINATES

ElieI has developed a method of making chiral α -hydroxy carbonyl compounds using a conformationally locked 1,3-oxathiane²³ and has used this method in the synthesis of both isomers of 2-acetoxycitramalate²⁴. In the general procedure as shown in Scheme 15, treatment of the oxathiane with *n*-BuLi followed by addition of an aldehyde forms exclusively the equatorially substituted product. Oxidation of the alcohol to the ketone followed by treatment with an alkyl Grignard reagent gave only the product which conforms to Cram's rule. The alcohol was then methylated and the chiral auxiliary removed oxidatively. Oxidation of the resultant aldehyde with Jones reagent followed by treatment with diazomethane gave methyl atrolactate methyl ether in 100% optical yield. In the citramalate synthesis²⁴ (Scheme 16) the menthol-derived oxathiane could afford either isomer of the dimethyl-2-

acetoxycitramalate in 51% yield over 7 steps in 96.6% e.e.

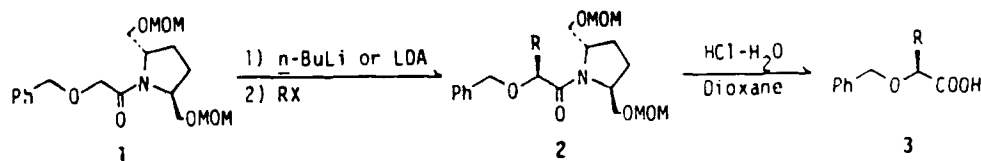


SCHEME 15: ELIEL'S METHOD USING LOCKED OXATHIANES



SCHEME 16: ELIEL'S CITRAMALATE SYNTHESIS

Katsuki developed the chiral auxiliary trans-2,5-bis(methoxymethoxymethyl)pyrrolidine which allows for diastereoselective alkylation of its N-benzyloxyacetyl derivative²⁵ (Scheme 17). Treatment of the amide with *n*-BuLi or LDA followed by alkylation with an alkyl halide gave the alkylated products in 65-92% yield with 96-98% d.e. Hydrolysis with refluxing 50:50 1M HCl/dioxane gave the free acid in 73-89% yield. In each case the (2*S*,5*S*)-auxiliary gave predominantly the (*S*)-products.

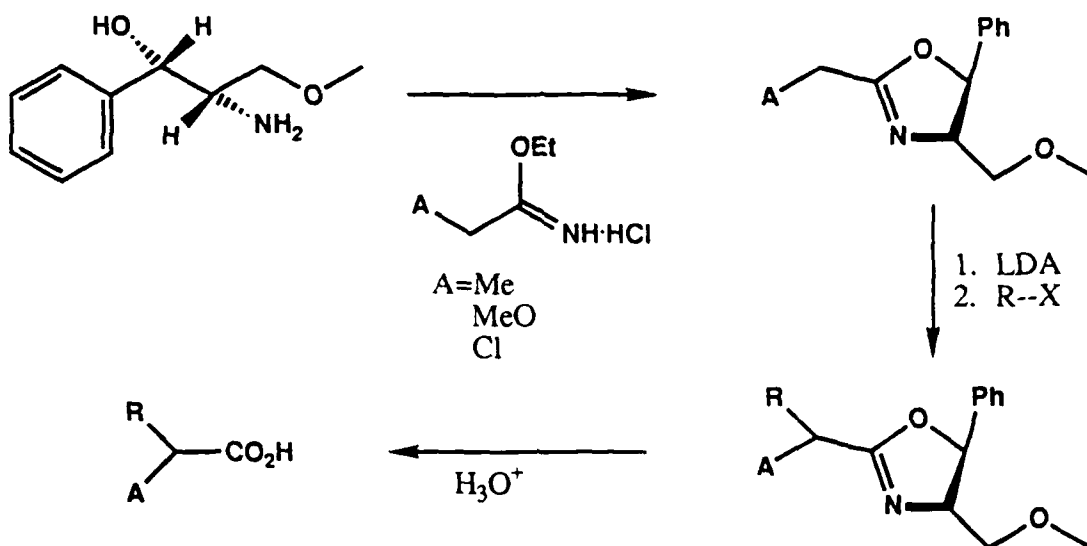


Asymmetric Alkylation of (2*S*,5*S*)-1 in THF and Subsequent Hydrolysis

Entry	RX	Base	Reaction Temp. (°C)	Alkylated Amide (2)			Hydrolyzed Product (3)		
				Yield (%)	[α] _D (EtOH)	%de	Yield (%)	[α] _D (EtOH)	Config.
1	CH ₃ I	<i>n</i> -BuLi	-78	92	-95° c=4.43	97	88	-86° c=0.96	<i>S</i>
2	PhCH ₂ Br	<i>n</i> -BuLi	-78	91	-38° c=5.45	98	89	-81° c=2.24	<i>S</i>
3	C ₄ H ₉ I	<i>n</i> -BuLi	-78~-20	77	-79° c=4.29	96	83	-73° c=1.19	<i>S</i>
4	C ₈ H ₁₇ I	LDA	-78~-20	72	-70° c=0.54	96	73	-55° c=0.41	<i>S</i>
5	PhCH ₂ O(CH ₂) ₆ I	LDA	-78~-20	65	-58° c=1.32	96	84	-45° c=1.30	<i>S</i>
6	(CH ₃) ₂ CHI	LDA	-78~-20	trace					
7	(CH ₃) ₂ CHOTf	LDA	-20	76	-63° c=0.95	97	65	-74° c=1.01	<i>S</i>

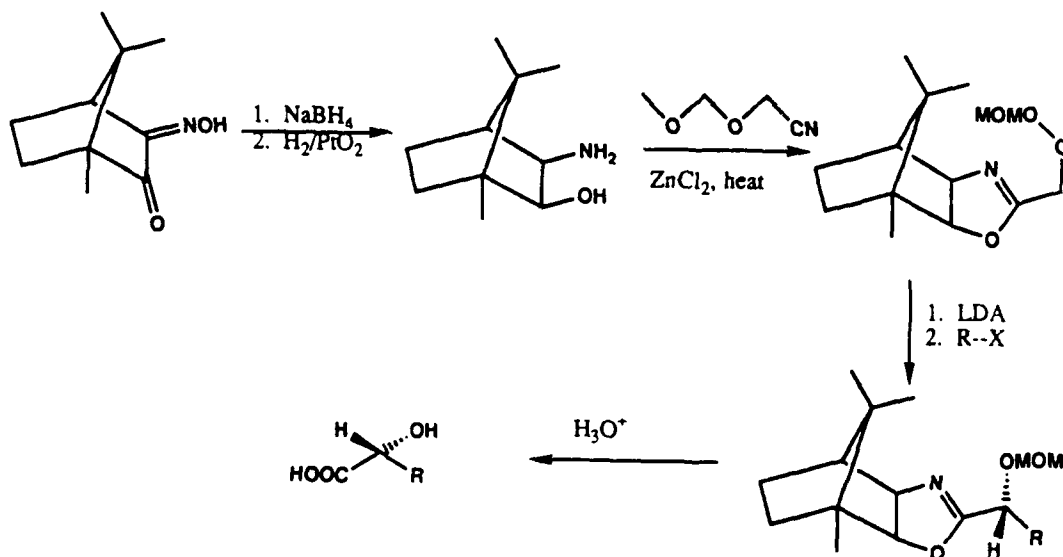
SCHEME 17: KATSUKI'S CHIRAL PYRROLIDINE METHOD

Meyers developed a method in 1974²⁶ to alkylate diastereoselectively using chiral oxazolines (Scheme 18). Unfortunately, his selectivities were low (11-42% d.e.'s) though the yields were high (90-97%).



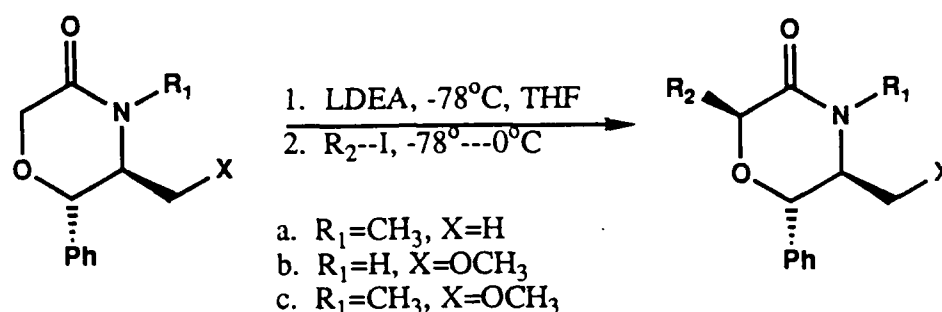
SCHEME 18: MEYERS' CHIRAL OXAZOLINE METHOD

Kelly modified Meyers' approach (Scheme 19) by using (+)-camphor to make the oxazoline²⁷. Upon alkylation Kelly got products in 26-72% yield with 77-92% e.e. In each of his alkylations the products had the (*R*) configuration.



SCHEME 19: KELLY'S METHOD USING CAMPHOR-DERIVED OXAZOLINES

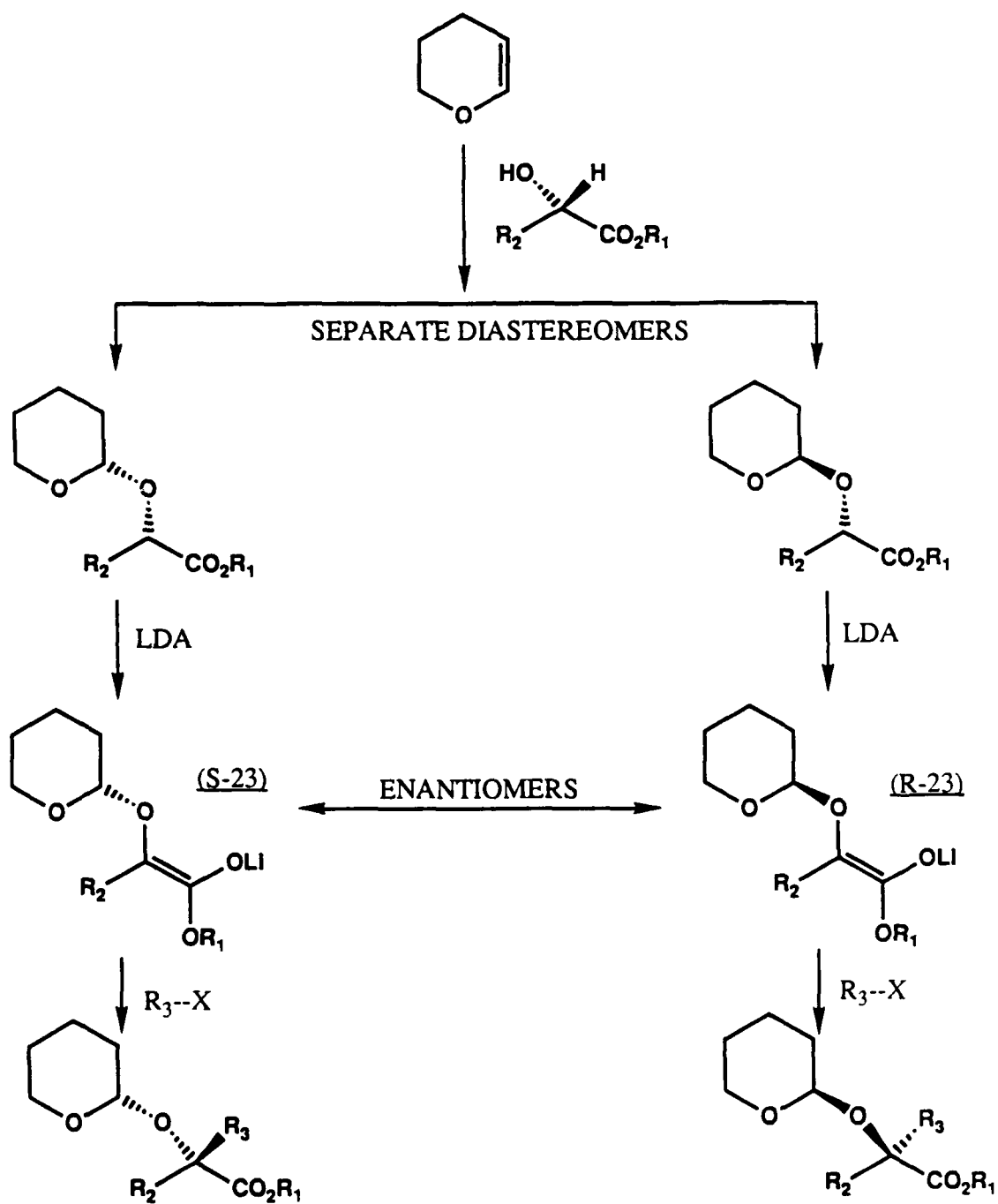
Newcomb and Bergbreiter also studied diastereoselective alkylation but by first forming a carboxamide so that the required enolate intermediate would be more stable (Scheme 20)²⁸. The carboxamides could be derived by reaction of a



SCHEME 20: NEWCOMB AND BERGBREITER'S METHOD

chiral hydroxy amine with either glycolic or lactic acid and could be either cyclic or acyclic. The alkylated products were obtained in 35-97% yields with d.e.'s ranging from 8-96%.

The final example of diastereoselective alkylation was performed by Noe²⁹ not on a simple α -hydroxy acid but on mercaptoacetic acid. Reaction of mercaptoacetic acid with a chiral lactol to form the thioacetal was followed by selective alkylation (Scheme 21) to form the alkylated product with (R) stereochemistry. Yields of the alkylation varied from 89-97% and the d.e.'s varied from 54-60%. The product diastereomers could be resolved as their methyl esters to afford enantiomerically pure products after hydrolysis. Noe's method is also very similar to the work discussed here in that a chiral acetal is used to direct the course of a diastereoselective



SCHEME 22: DIASTEREOSELECTIVE ALKYLATIONS OF ESTER ENOLATE THP ETHERS

Chapter 1. The separation of the diastereomers results in two pyranosides whose only difference is the chirality of the anomeric center (along with any linked stereocenters). It was hoped that the chirality of the anomeric center would direct the course of the subsequent alkylation. Deprotonation of the ester-acetals was accomplished using LDA in THF at -78°C to form the ester enolates (S)-23 and (R)-23. The Z enolate geometry (as shown) was assumed by Heathcock³⁰ to be the predominant form. These enolates are an enantiomeric pair which should react with electrophiles in similar (but enantiomeric) fashion. The results of alkylations of these enolates with a variety of electrophiles are summarized in Table 2.

A number of reaction variables were studied to try to maximize the yield and diastereoselectivity of the alkylation. Variables which were studied were the alkylating agent (alkyl group and leaving group), ester alcohol group (R_1), appendage (R_2), solvent effects, and the effect of HMPA catalyst. Results of these studies are summarized below.

Alkylating Agent Effects:

As shown in the table, alkylation with alkyl groups which can stabilize the transition state (allyl iodide and benzyl bromide, Entries 2 and 8 respectively) proceeded in good yields in THF solvent and without the use of a catalyst. However, attempts at alkylations using simple (unactivated) alkyl groups were very sluggish at -78°C and gave only

Table 2. Diastereoselective Alkylations of Enolates Derived from Alkyl Hexyl 3,4,5,6-Tetrahydro-2g-Pyranosides and Related Compounds.

Entry	Enolate ^a	R ₁	R ₂	Solvent	R ₃ ^b	Products	Yields, %	Diastereomer Ratio, a:b or c:d
1	(S)-23a	CH ₃	CH ₃	THF	CH ₂ =CHCH ₂ Cl	24a, 24b	no reaction	—
2	(S)-23a	CH ₃	CH ₃	THF	CH ₂ =CHCH ₂ I	24a, 24b	85	4:1
3	(S)-23a	CH ₃	CH ₃	PhCH ₃	CH ₂ =CHCH ₂ I	24a, 24b	37	6:1
4	(S)-23b	CH ₂ CH ₃	CH ₃	THF	CH ₂ =CHCH ₂ I	25a, 25b	85	5:1
5	(S)-23c	CH(CH ₃) ₂	CH ₃	THF	CH ₂ =CHCH ₂ I	26a, 26b	85	6:1
6	(R/S)-23d	C(CH ₃) ₃	CH ₃	THF	CH ₂ =CHCH ₂ I	27a/27c, 27b/27d	92	4:1
7	(S)-23c	CH(CH ₃) ₂	CH ₃	THF	CH ₂ =CHCH ₂ Br	26a, 26b	66	2:1
8	(R)-23a	CH ₃	CH ₃	THF	PhCH ₂ Br	28c, 28d	93	4:1
9	(S)-23a	CH ₃	CH ₃	THF/HMPA	PhCH ₂ Br	28a, 28b	92	3:1
10	(R/S)-23a	CH ₃	CH ₃	THF	CH ₃ I	29a, 29c	50	—
11	(R/S)-23a	CH ₃	CH ₃	THF	CH ₃ (CH ₂) ₈ I	30a/30c, 30b/30d	16	not determined
12	(R/S)-23a	CH ₃	CH ₃	THF/HMPA	CH ₃ (CH ₂) ₈ I	30a/30c, 30b/30d	59	3:2
13	(S)-23a	CH ₃	CH ₃	THF/HMPA	CH ₃ C(CH ₃)(CH ₂) ₃ I	31a, 31b	83	2:1
14	(R)-23a	CH ₃	CH ₃	THF/HMPA	CH ₃ C(CH ₃)(CH ₂) ₃ I	31c, 31d	84	3:2
15	(R/S)-23a	CH ₃	CH ₃	PhCH ₃	CH ₃ C(CH ₃)(CH ₂) ₃ I	31a/31c, 31b/31d	14	4:1
16	(R/S)-23c	CH(CH ₃) ₂	CH ₃	THF/HMPA	CH ₃ C(CH ₃)(CH ₂) ₃ I	32a/32c, 32b/32d	40	3:1
17	(S)-23a	CH ₃	CH ₂ Ph	THF	CH ₂ =CHCH ₂ I	33a, 33b	60	4:1
18	(R)-23a	CH ₃	CH ₂ Ph	THF	CH ₂ =CHCH ₂ I	33c, 33d	50	4:1
19	(S)-23f	CH ₃	CH ₂ CH(CH ₃) ₂	THF	CH ₂ =CHCH ₂ I	34a, 34b	50	1:1
20	(R)-23f	CH ₃	CH ₂ CH(CH ₃) ₂	THF	CH ₂ =CHCH ₂ I	34c, 34d	54	1:1
21	(S)-23g	CH ₃	CH ₂ C(CH ₃) ₂	THF	CH ₂ =CHCH ₂ I	35a, 35b	30	3:1
22	(S)-23g	CH ₃	CH ₂ C(CH ₃) ₂	THF/HMPA	CH ₂ =CHCH ₂ I	35a, 35b	37	2:1
23	(S)-23h	CH ₃	Ph	THF	CH ₂ =CHCH ₂ I	36a, 36b	82	12:1
24	(S)-23h	CH ₃	Ph	THF/HMPA	CH ₃ I	37a, 37b	89	5:1

(a) The Z enolate geometry is presumed; see Ref. 30.

(b) Determined by 62.9-MHz ¹³C NMR spectroscopy.(c) The separation factor, α, is the ratio of R_f values for diastereomers a and b (or c and d) on 0.25 mm silica gel on analytical tic plates (Merck, 70-250 mesh) eluted with 20% ethyl acetate in hexanes.

moderate to poor yields (Entries 10 and 11) if no catalyst was used. The nature of the leaving group also affected the alkylation: allyl chloride failed (Entry 1) presumably due to lack of reactivity of the chloride. Alkylation with allyl bromide (Entry 7) was successful though with somewhat low yield (66%) while alkylation with allyl iodide gave the alkylated products in 85% yield (Entry 2). This indicates the expected trend that the reaction would proceed faster as the leaving group improves.

Ester Alcohol (R_1) Effects:

Changes in the ester from methyl (Entry 2) to larger alkyl groups (ethyl, Entry 4; isopropyl, Entry 5; and t-butyl, Entry 6) demonstrated that to a point the larger alkyl groups gave somewhat better diastereoselectivity for the alkylation. The limit was reached at the isopropyl group and the t-butyl group gave somewhat lower diastereoselectivity. R_1 had little or no effect on the yield of the alkylation.

Appendage (R_2) Effects:

The R_2 appendage was the most significant variable affecting both the yield and the diastereoselectivity of the alkylation. While in some cases the yield dropped as low as 30-40% (Entries 19, 21, and 22), in other cases the yield was quite high (80-90%, see Entries 2, 6, 23, and 24). Bulkier appendages in general gave lower yields. The effect of R_2 on the diastereoselectivity was more dramatic. While most often

moderate diastereoselectivity was obtained (3-5:1) in the cases where R_2 was isobutyl (Entries 19 and 20) the diastereomer ratio was 1:1 and where R_2 was phenyl (Entry 23) the ratio was 12:1! The more sterically demanding appendages apparently either partially blocked the enolate face which was normally alkylated or caused the lithium enolate coordination with the THP oxygen to be broken up (to relieve steric strain) thus allowing alkylation of the other face.

Solvent Effects:

The alkylation reactions were typically carried out in THF and the solvent molecules were assumed to solvate the lithium enolate by complexing to the lithium. Attempts at running the alkylations in the non-coordinating solvent toluene showed that the diastereoselectivity increased but that the reaction proceeded much more slowly and in lower yield (compare Entries 3 and 15 with Entries 2 and 14). No experiments were run in mixed solvent systems though they may have given the increased diastereoselectivity without the high cost in yield.

Catalyst Effects:

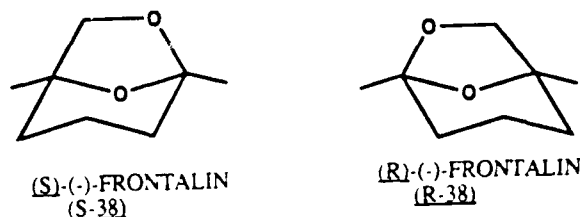
As mentioned above, reactions with simple alkyl halides required the presence of a catalyst in order to proceed in reasonable yield (compare Entries 11 and 12). The catalyst used was hexamethylphosphoramide (HMPA); it coordinates to the lithium cation and thus renders the enolate more reactive

toward electrophiles. In alkylations with activated alkyl halides however the presence of catalyst had little or no effect on the yield of the reaction but did lower the diastereoselectivity somewhat (compare Entries 8 and 21 with Entries 9 and 22).

A final important result of this alkylation study is that often the product diastereomers from the alkylation were themselves separable by column chromatography. As shown by the α values in Table 2 the only cases where inseparable products were obtained were allylation of lactate-derived enolates (Entries 2-7) and the reaction between the enolate derived from isopropyl lactate and 5-iodo-2-methyl-1-pentene (Entry 16). In every other case the alkylated products could be separated by column chromatography to give enantiomerically pure products.

The utility of this method for organic synthesis now becomes readily apparent. By resolving the diastereomers of THP-protected α -hydroxyesters one can selectively alkylate their enolates and get enantiomerically pure α -alkyl- α -hydroxy esters after resolution and hydrolysis (assuming the alkylated products are separable). Since both of the enantiomeric enolates (S)-23 and (R)-23 are equally available (by resolution of the diastereomers and treatment with LDA), both of the product enantiomers would also be equally available. Finally, the results are predictable since the (S) enolate is

alkylated selectively on the Re face and the (R) enolate is alkylated selectively on the Si face (as demonstrated below). To demonstrate the utility of this method in synthesis the natural product (-)-frontalin 38 was chosen.

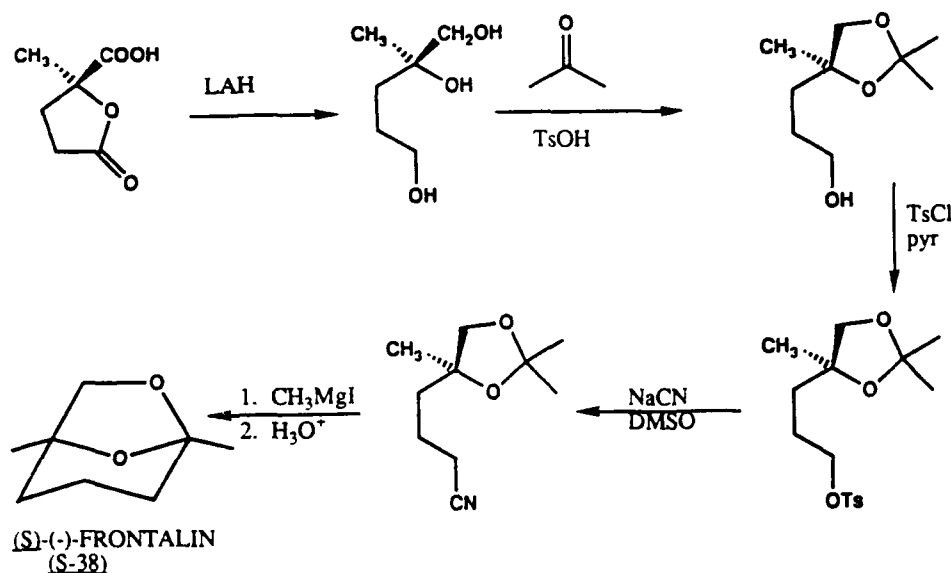


C. PRIOR SYNTHESSES OF FRONTALIN

Frontalin was first isolated by Kinzer³¹ and is a component of the aggregation pheromone of the southern pine beetle Dendroctonus frontalis Zimmerman and the western pine beetle Dendroctonus brevicomis Le Conte. Mori³² synthesized both enantiomers of frontalin and has shown that the (1S,5R) configuration (S-38) is biologically active while its antipode (R-38) is inactive. It has been a frequent synthetic target both in racemic form and as the optically active materials. A summary of prior syntheses of the optically active frontalin is presented below.

The first synthesis of optically active frontalin was done by Mori³² and is outlined in Scheme 23. Mori first synthesized the racemic lactonic acid (from levulinic acid) and resolved the enantiomers as their quinine and cinchonine

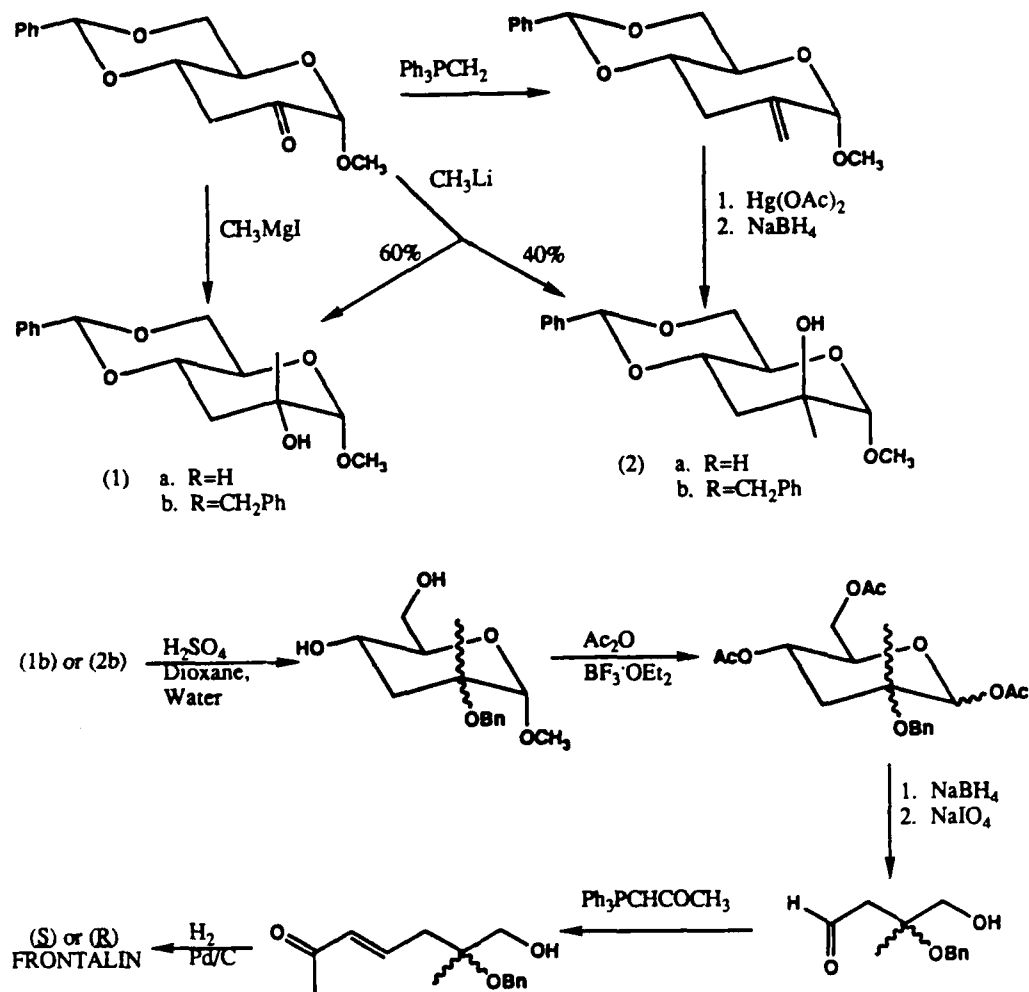
salts to obtain the starting material for the synthesis. Reduction with LAH gave the triol which was then dissolved in



SCHEME 23: MORI'S FRONTALIN SYNTHESIS

acetone and treated with *p*-TsOH to give the acetonide. The acetonide was tosylated and then treated with NaCN in DMSO to give the nitrile. Addition of MeMgI and subsequent acidification produced optically pure frontalin. Both frontalin enantiomers were produced by this method in roughly 7% yield over 5 steps (starting from the optically pure lactone).

The next synthesis was done by Fraser-Reid³³ and is outlined in Scheme 24. Starting with the ketone (derived from methyl- α -D-glucopyranoside in 4 steps) Fraser-Reid was able to synthesize either or both enantiomers of frontalin in 13% yield after 7 steps. The key to this synthesis was the

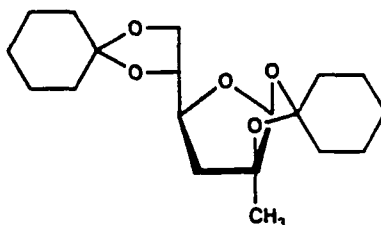


SCHEME 24: FRASER-REID'S FRONTALIN SYNTHESIS

diastereoselective conversion of the ketone to the tertiary alcohol by addition of the methyl group. By exploiting the axial orientation of the methoxy substituent at the anomeric center he was able to selectively deliver reagents to the top face of the ketone (or alkene) and thus prepare the chiral center in optically pure form after chromatography or

recrystallization. A later modification to his procedure³⁴ started with methyl 2,6-di-O-benzoyl- α -D-glucopyranoside and gave either optically pure product in 5% yield over 16 steps.

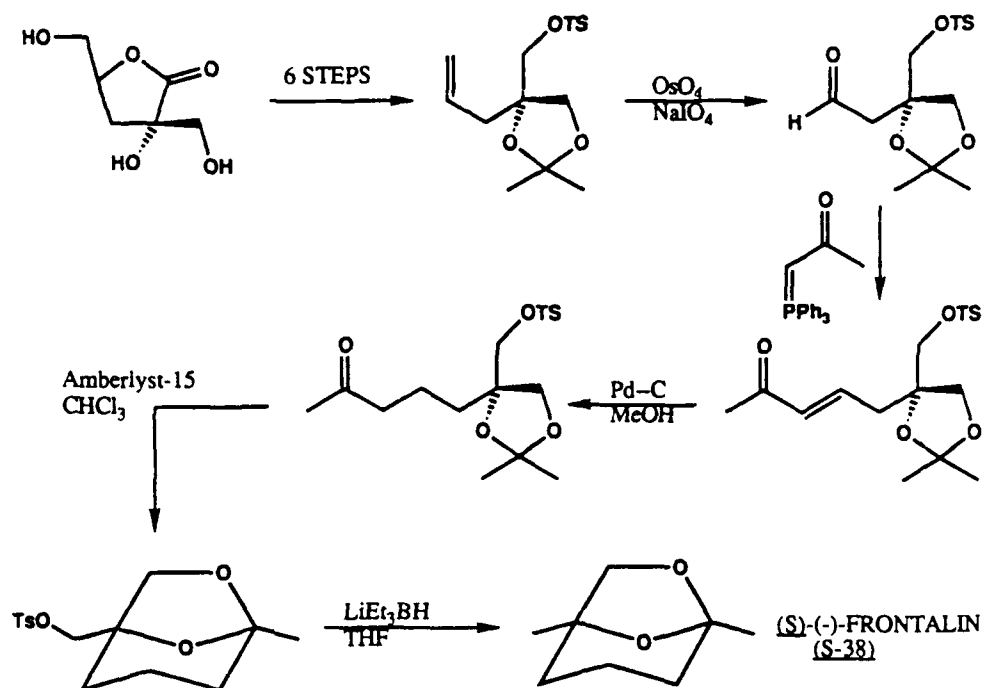
A second "carve-up-a-sugar" approach was reported by Emoto³⁵. Starting from 1,2:5,6-di-O-cyclohexylidene-3-deoxy-2-C-methyl- β -D-arabino-hexofuranose (shown below) which was prepared from D-glucose (4 steps, <47% yield) Emoto was able



to synthesize (S)-frontalin in 18% yield over 10 steps (<7% yield over 14 steps from D-glucose).

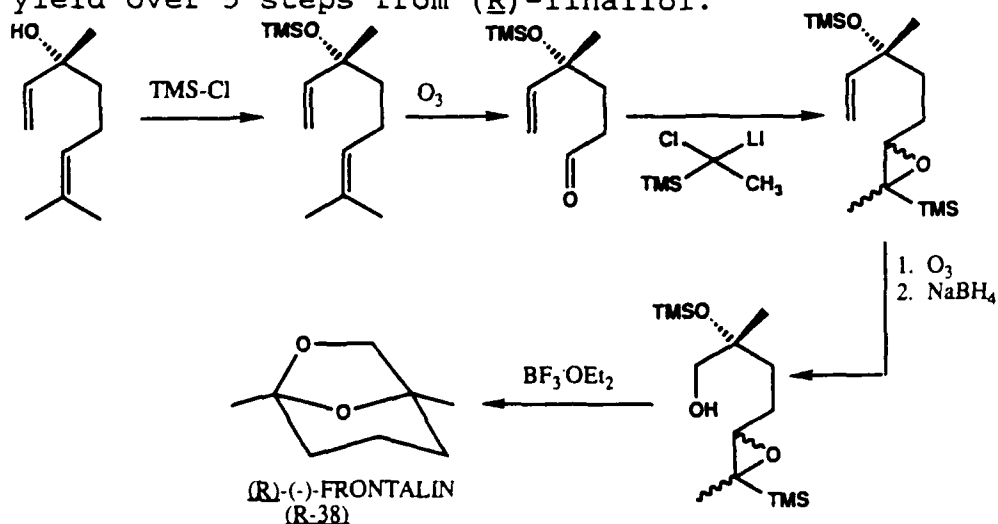
A final method which relies on the chirality inherent in natural sugars was developed by Monneret^{36,37} and begins with α -D-isosaccharino-1,4-lactone (prepared by alkaline treatment of lactose). As outlined in Scheme 25, Monneret was able to synthesize (S)-frontalin in 17% yield over 10 steps from the lactone. A slight modification of this procedure gave (R)-frontalin in 8% yield over 12 steps. Both products were obtained in optically pure form.

Magnus demonstrated the use of a new organosilicon reagent in organic synthesis when he used it to synthesize (R)-frontalin from (3R)-(-)-linalool^{38,39}. As outlined in



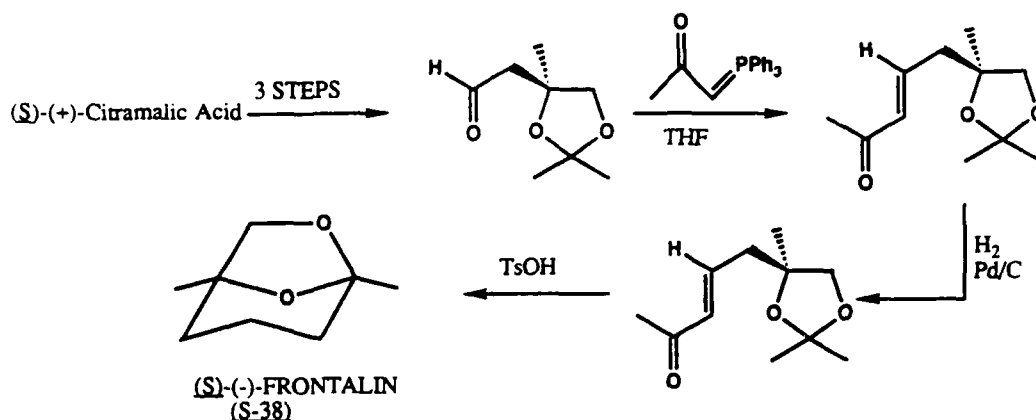
SCHEME 25: MONNERET'S FRONTALIN SYNTHESIS

Scheme 26 Magnus was able to synthesize (R)-frontalin in 23-29% yield over 5 steps from (R)-linallol.



SCHEME 26: MAGNUS' FRONTALIN SYNTHESIS

A final synthesis of (S)-frontalin which relies on the stereochemistry present in natural products was developed by Barner⁴⁰. Starting from (S)-(+)-citramalic acid (expensive) Barner was able to synthesize (S)-frontalin in 14% yield over 6 steps (Scheme 27).

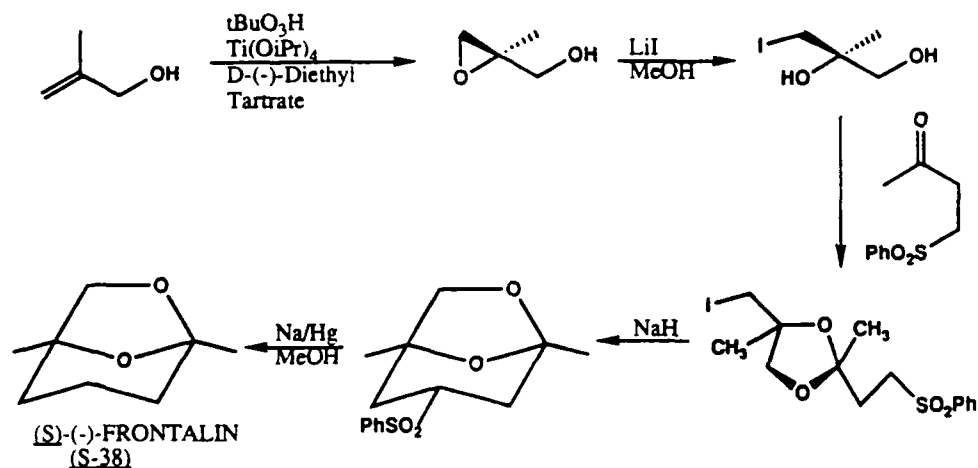


SCHEME 27: BARNER'S FRONTALIN SYNTHESIS

Two separate authors were able to synthesize (S)-(-)-frontalin using fermentation with baker's yeast. Fuganti⁴¹ used the yeast with α -methylcinnamaldehyde in his synthesis to produce frontalin in 1.6% yield over 9 steps with 86% e.e.; likewise Fujisawa⁴² used baker's yeast with (S)-ethyl-2-cyclopentanonecarboxylthioate to produce optically pure frontalin in 13% yield over 9 steps.

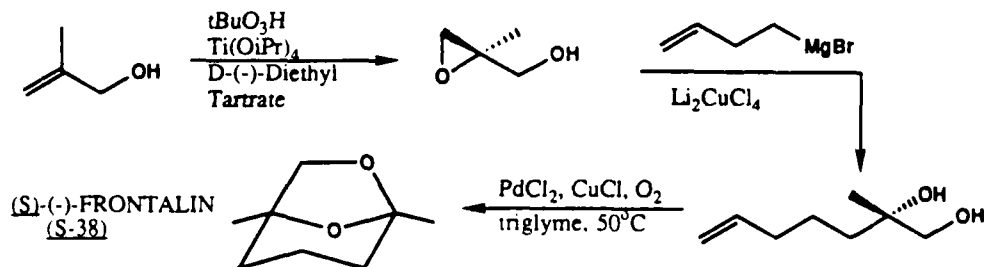
A very popular general method for the synthesis of the frontalin enantiomers uses Sharpless epoxidation to generate the required chirality. This method was first used by Scharf⁴³ to synthesize (S)-frontalin in 2.5% yield over 7 steps. He

later improved the procedure⁴⁴ (Scheme 28) to give frontalin in 10% yield over 5 steps with an e.e. of 92%. The starting material for the epoxidation in both these syntheses was methallyl alcohol.



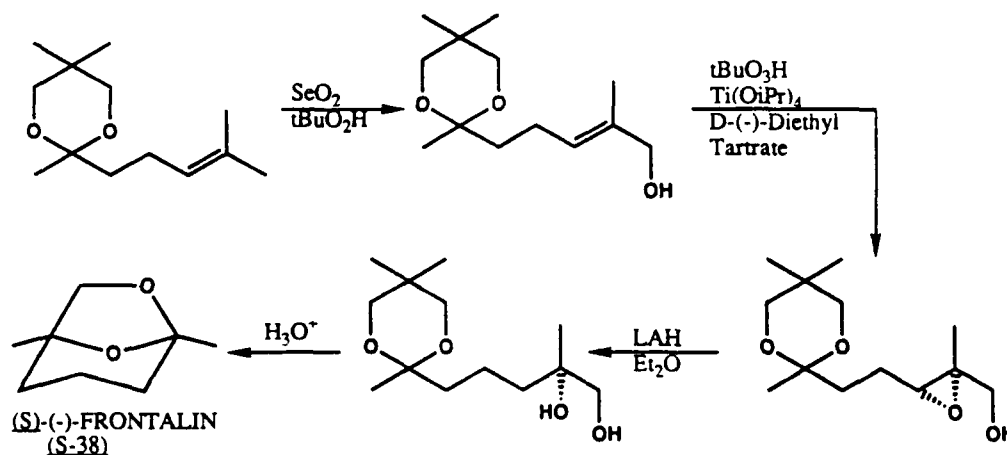
SCHEME 28: SHARF'S FRONTALIN SYNTHESIS

A later synthesis of the frontalin enantiomers using Sharpless epoxidation of methallyl alcohol was performed by Hosokawa⁴⁵. This short, fast synthesis (Scheme 29) afforded (S)-frontalin with 90% e.e. in 28% yield over 3 steps. (R)-Frontalin was likewise obtained but with 83% e.e.



SCHEME 29: HOSOKAWA'S FRONTALIN SYNTHESIS

Lee also developed a method for synthesizing both enantiomers of frontalin using Sharpless epoxidation (Scheme 30)⁴⁶. Starting from 6-methylhept-5-en-2-one Lee could synthesize optically pure (S)-frontalin in "good" yield over 5 steps or (R)-frontalin in 67% yield (also optically pure).



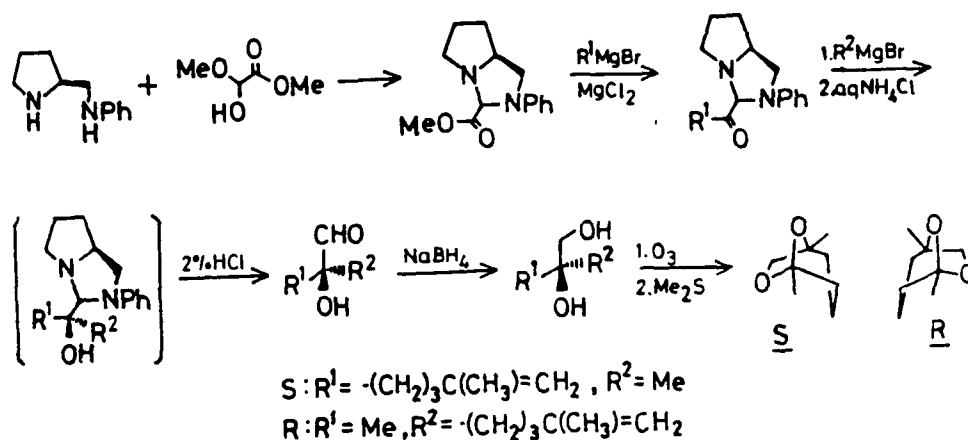
SCHEME 30: LEE'S FRONTALIN SYNTHESIS

Another use of Sharpless epoxidation in frontalin synthesis was by Johnston⁴⁷ who started with (E)-2-methyl-2,6-heptadien-1-ol (Scheme 31). This 6-step reaction sequence could provide (S)-frontalin with 97% e.e. or (R)-frontalin with 89-93% e.e. in 50% yield overall. This synthesis is also notable in that it requires no chromatographic purification of the intermediates.

The final example of synthesis of (S)-frontalin using Sharpless epoxidation was done by Yadav⁴⁸ and is outlined in (Scheme 32). This 5-step synthesis begins with the alkylation

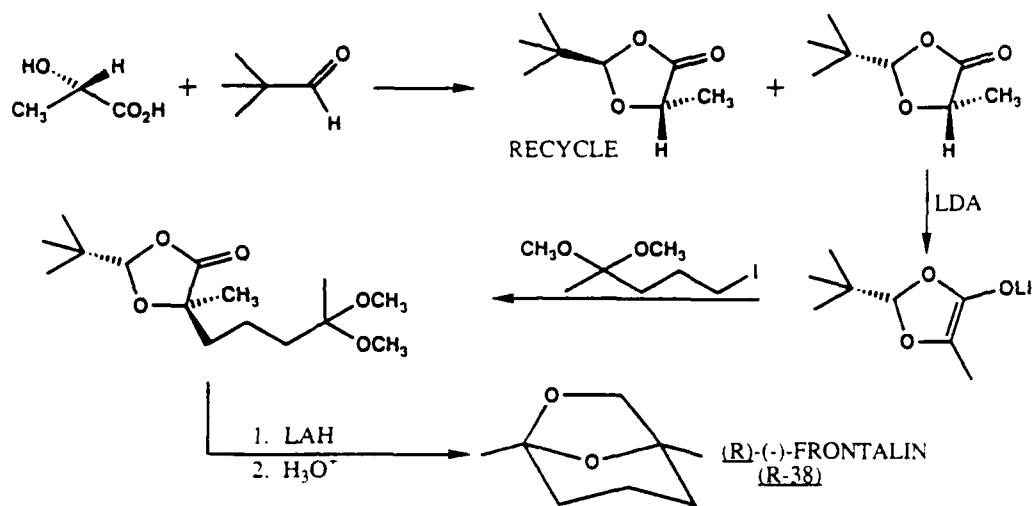
of diethyl malonate with 5-bromopentan-2-one ethylene ketal and affords the optically pure product in 42% yield.

The final four syntheses of frontalinalin to be discussed all rely on chiral auxiliaries to direct diastereoselective alkylations. They are thus closely related to the method we have developed and give a good basis for comparison. The first was developed by Sakito⁴⁹ and uses (S)-2-(anilinomethyl) pyrrolidine as the chiral auxiliary (Scheme 33). The 6-step synthesis gives (S)-frontalinalin in 40% yield with an e.e. of 86% or (R)-frontalinalin in 47% yield with an e.e. of 100% depending on the order of addition of the alkylating agents.



SCHEME 33: SAKITO'S FRONTALIN SYNTHESIS

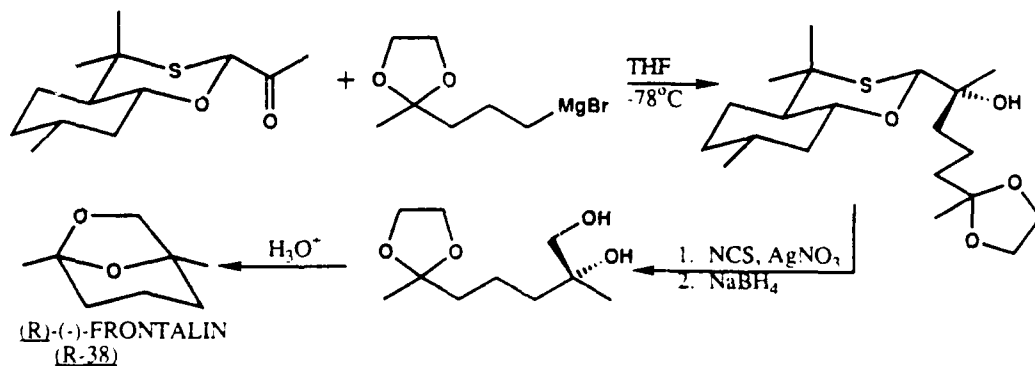
Seebach used his pivaldehyde-based chiral auxiliary with (S)-lactic acid in his synthesis of the frontalinalin enantiomers (Scheme 34)⁵⁰. Using (S)-lactic acid gave (R)-frontalinalin with 100% optical purity in 73% yield over 5 steps. Synthesis of (S)-frontalinalin in comparable yield and optical purity was also



SCHEME 34: SEEBACH'S FRONTALIN SYNTHESIS

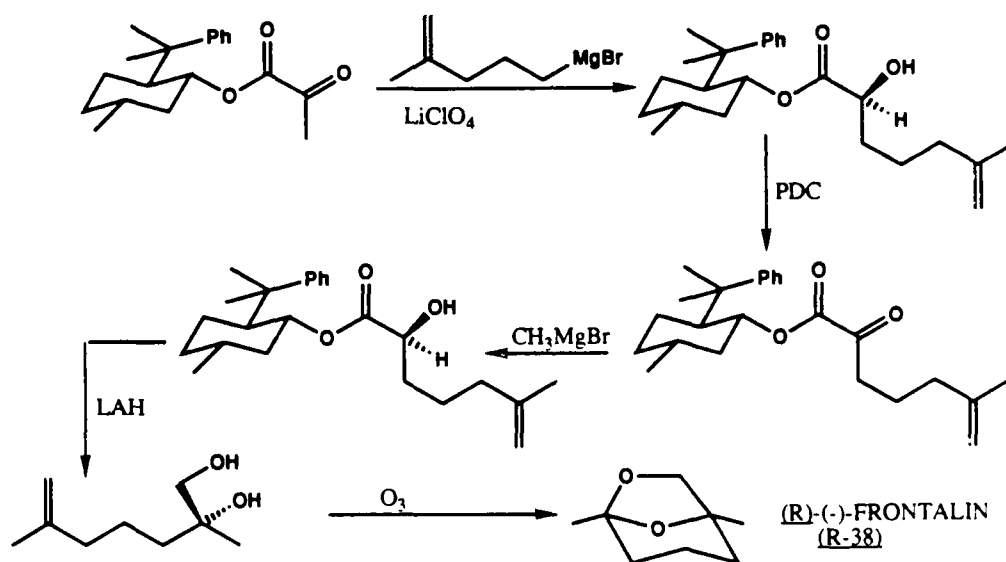
achieved by starting with (R)-lactic acid.

Eliei was also able to synthesize both enantiomers of frontalin using his menthol-derived 1,3-oxathiane auxiliary⁵¹. The 7-step synthesis (not shown) could be used to produce either (R)- or (S)-frontalin in 28-34% yield with 96% e.e. A simplified procedure (Scheme 35) also was used which gave (R)-frontalin in 42% yield with 91% e.e. or (S)-frontalin with 70% e.e. (comparable yield) over 3 steps.



SCHEME 35: ELIEI'S SIMPLIFIED FRONTALIN SYNTHESIS

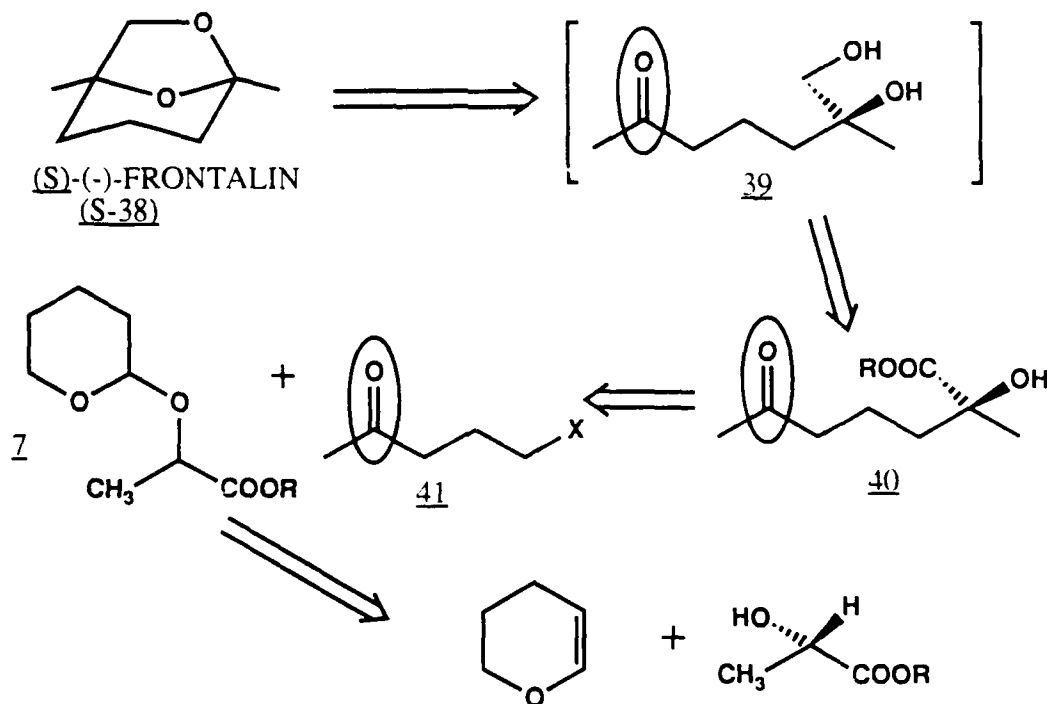
The final synthesis of frontalin using a chiral auxiliary to be discussed was performed by Whitesell⁵². Starting from the pyruvate ester of 8-phenylmenthol the 3-step method allows for synthesis of (S)-frontalin with optical purity in 37% yield. To obtain (R)-frontalin required starting with the glyoxylate ester of 8-phenylmenthol and 5 steps (Scheme 36). The overall yield of optically pure (R)-frontalin was only 4.1%, however, due to low yields (<40%) for both the alkylation steps.



SCHEME 36: WHITESELL'S (R)-FRONTALIN SYNTHESIS

D. FRONTALIN SYNTHESIS BY DIASTEREOSELECTIVE ALKYLATION OF α -HYDROXY ESTER TETRAHYDROPYRANYL ETHERS.

A retrosynthetic analysis of (S)-frontalin using our method is outlined in Scheme 37. Ring opening of the bicyclic ketal gives the ketone diol 39 which could be obtained by



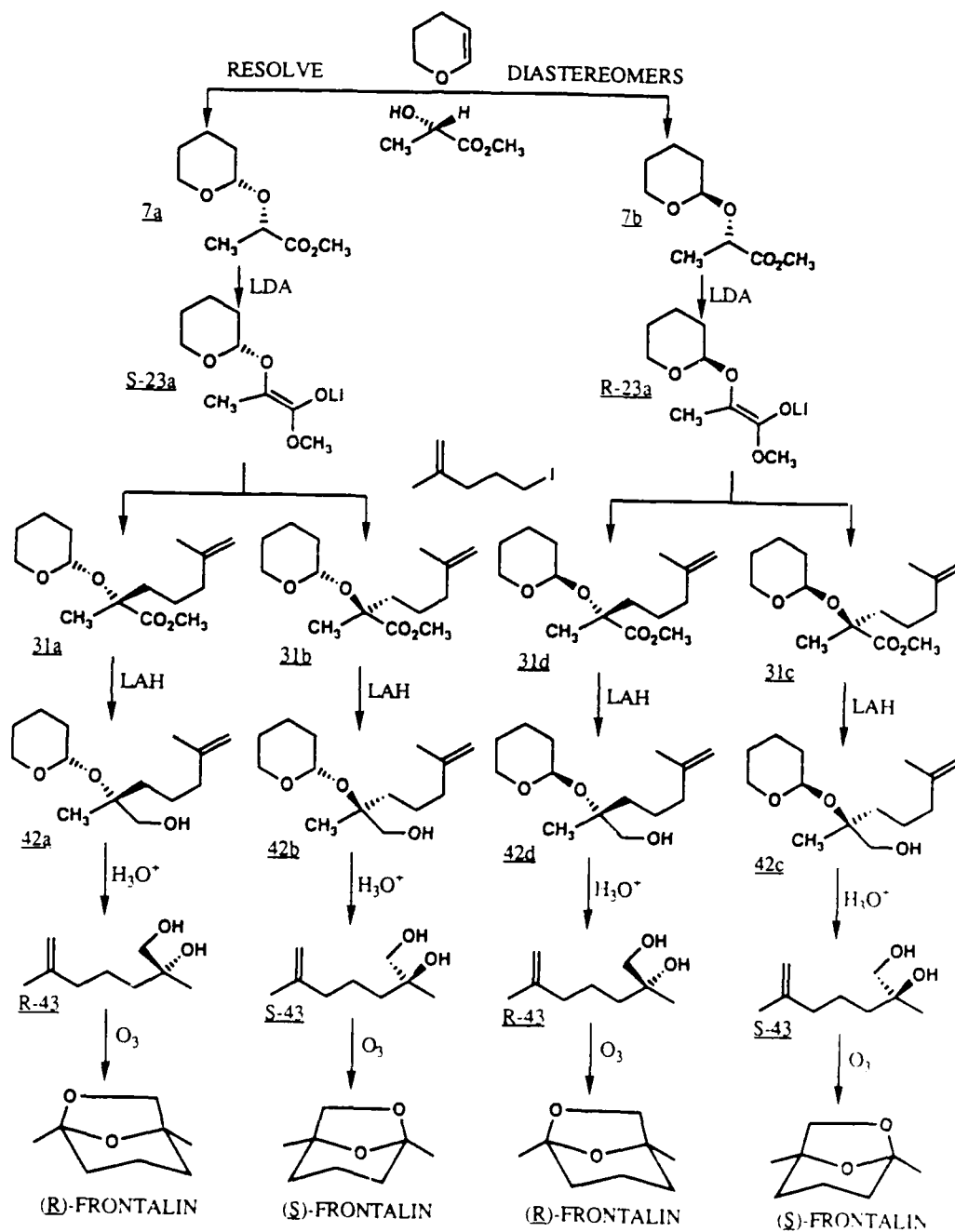
SCHEME 37: RETROSYNTHETIC ANALYSIS OF FRONTALIN

reduction of the corresponding protected keto ester 40. The keto ester could be generated diastereoselectively by alkylation of one of the THP-lactate diastereomers 7 with the protected alkyl halide 41. The THP-lactate diastereomer synthesis from dihydropyran and (S)-alkyl lactate has already been described.

Early attempts at the synthesis of frontalin as outlined in the retrosynthetic analysis failed at the alkylation step when the alkylating agent used was the ethylene ketal of 5-iodo-2-pentanone. The failure of this reaction may have been due either to the lack of use of catalyst to speed up the

reaction or to sensitivity of the alkylating agent to the reaction conditions. In either case, a decision was made to use 5-iodo-2-methyl-1-pentene as the alkylating agent to avoid the use of a protected ketone. Ozonolysis of the alkene in a later step would then afford the ketone.

The actual method used for the synthesis of both enantiomers of frontaline is outlined in Scheme 38. The reaction of DHP with (S)-methyl lactate in CH_2Cl_2 using PPTS catalyst afforded the less polar (S,S) diastereomer 7a and more polar (R,S) diastereomer 7b each in 49% yield after separation. The separation by gravity driven column chromatography required 2 passes on 200g of silica gel 60 as described in Chapter 1. When 7b was treated with LDA in THF at -78°C the lithium enolate (R)-23a was formed which was then alkylated with the 5-iodo-2-methyl-1-pentene in the presence of 2.4 equivalents of HMPA to give the alkylated products 31c and 31d in 84% combined yield in a 3 to 2 ratio. Prior examination of molecular models led to the prediction that the (R)-enolate would be selectively alkylated on the Si face if the lithium coordinated to both the enolate and to the oxygen in the THP ring, primarily due to blocking of the Re face by the hydrogen at the anomeric center. Note that the major product of the alkylation of the (R)-enolate (R)-23a is as expected the product of alkylation on the Si face while the minor product is the result of alkylation on the Re face.



SCHEME 38: ACTUAL FRONTALIN SYNTHESIS

These product diastereomers 31c and 31d were separated by column chromatography. The ester 31d was then reduced to the

alcohol 42d using LAH in diethyl ether in 91% yield. Hydrolysis of the THP protecting group of 42d using 1% HCl/9% H₂O/90% CH₃OH gave the free diol (R)-43 in 93% yield after 2 hours at 0°C. This diol was identical with material prepared by Whitesell⁵² by NMR, IR and optical rotation. Following Whitesell's procedure for ozonolysis of (R)-43 with reductive workup gave (R)-frontalin (R-38) in 66% yield. Treatment of the ester 31c with LAH followed by acid hydrolysis (without chromatographic purification of the alcohol 42c gave the free diol (S)-43 in 89% yield for the 2 steps. The product, identical with (R)-43 but with opposite rotation, was then ozonized to give (S)-frontalin (S-38) in 66% yield after column chromatography and preparative GLC. The optical rotation of the (S)-frontalin was -50.3° which corresponds to optical purity.

In a manner analogous to the procedure just described the lactate pyranoside 7a was selectively alkylated on the Re face to give the alkylated products 31a and 31b in a 2 to 1 ratio in 83% combined yield. Each of these products were then reduced with LAH, hydrolyzed with acid, and treated with ozone to afford the optically pure frontalin enantiomers shown. An important point to note is that while the lactate pyranoside 7b gave (S)-frontalin as the major product and (R)-frontalin as the minor product the opposite was true for the pyranoside 7a. This result actually is what would be expected due to the

enantiomeric nature of the intermediate enolates (R)-23 and (S)-23.

By combining the reaction pathways as shown the ultimate result of this synthesis is optically pure (S)-frontalin in 23.1% yield and optically pure (R)-frontalin in 22.7% yield (combined yield: 45.8%) over 5 steps starting from dihydropyran and (S)-methyl lactate. A comparison of this method with the prior syntheses described above is presented in Table 3.

Table 3. Comparison of Frontalin Syntheses

Author	Starting Material	Steps	Yield	Enant-iomer	$[\alpha]_D$
Mori	(R)-2-Hydroxy-2-methyl pentane-1,5-dioic acid 5-->2 lactone	5	7.6%	R	+53.4
		5	7.2%	S	-52
Fraser-Reid	Methyl α -D-glucopyranoside	11	<13%	R	+51.3
		11	<13%	S	-50.7
Fraser-Reid	Methyl 2,6-di-O-benzoyl- α -D-glucopyranoside	16	5%	S	-50.7
Emoto	D-Glucose	14	<7%	S	-54.4
Monneret	α -D-Isosaccharino-1,4-lactone	10	17%	S	-52
Monneret	α -D-Isosaccharino-1,4-lactone	11	12%	S	-52
		12	8%	R	+52
Magnus	(3R)-(-)-Linalool	5	26%	R	unk
Barner	(S)-(+)-Citramalic acid	6	14%	S	-55.5
Fuganti	α -Methylcinnamaldehyde	9	1.6%	S	-45

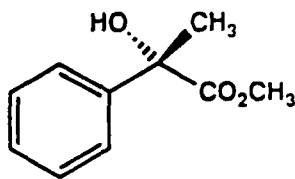
Table 3. Comparison of Frontalin Syntheses (cont)

Author	Starting Material	Steps	Yield	Enant- iomer	$[\alpha]_D$
Fujisawa	S-Ethyl-2-cyclopentan- onecarboxylthioate	9	13%	S	-51.7
Scharf	Methallyl alcohol	7	2.5%	S	-53.6
Scharf	Methallyl alcohol	5	10%	S	-49.4
		5	10%	R	+50.6
Hosokawa	Methallyl alcohol	3	28%	S	-50.9
		3	28%	R	+45.9
Lee	6-Methylhept-5-en-2-one	5	good	S	-51.8
		5	67%	R	+52.4
Johnston	(E)-2-Methyl-2,6-hepta- diene-1-ol	6	50%	S	-52.9
		6	50%	R	+50.7
Yadav	Diethyl malonate	5	42%	S	-51.5
Sakito	(S)-2-(Anilinomethyl) pyrrolidine	8	40%	S	-45.5
		8	47%	R	+54.3
Seebach	(R)-Lactic acid	4	73%	S	-53.5
	(S)-Lactic acid	4	73%	R	+53.4
Eliei	Chiral 1,3-oxathiane	3	42%	S	-37.8
		3	42%	R	+49.1
		7	34%	S	-51.8
		7	26%	R	+51.8
Whitesell	8-Phenylmenthyl pyruvate	3	37%	S	-54.8
	8-Phenylmenthyl gly- oxylate	5	4.1%	R	+54.3

This Method	(S)-Methyl lactate	5	23%	S	-50.3
		and	23%	R	+50.3

As a further evaluation of the use of this method in synthesis the product diastereomer 37a from methylation of (S)-3h (the enolate formed from the less polar diastereomer of the (S)-methyl mandelate tetrahydropyranoside) was subjected

to acid hydrolysis to give (S)-(+)-methyl atrolactate 44 in 95% yield with an specific rotation $[\alpha]_D^{27} +4.92$ (\pm 2.84 EtOH). This value is in excellent agreement with material prepared by Bonner⁵³ ($[\alpha]_D^{25} +5.0$, \pm 4.9, EtOH).

44

EXPERIMENTAL

GENERAL PROCEDURE FOR ALKYLATION OF THE PYRANOSIDES

Diisopropylamine (distilled from calcium hydride, 160 mg, 1.6 mmol) was dissolved in dry THF (10 mL) in a flame-dried 25 mL flask under argon. The solution was cooled to 0°C and n-butyllithium (0.9 mL of 1.6M solution in hexanes, 1.4 mmol) was added via syringe. The reaction was stirred for 20 minutes, cooled to -78°C, and the THP-protected α -hydroxy ester (200 mg, 1 mmol) was added via syringe. After stirring for 1 hour the alkylating agent (1-3 equivalents) was added via syringe. Progress of the reaction was followed by TLC. The reaction was quenched at -78°C with sat NaHCO₃ (10 mL), diluted with diethyl ether (100 mL), the layers separated, and the ether phase dried with MgSO₄ (5g), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on silica gel 60 eluted with 10% EtOAc/hexanes to afford the products as colorless oils.

Methyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate (24a and 24b, Entry 2).

Alkylation of (S)-3a with 2.7 equivalents of allyl iodide afforded a 4 to 1 ratio of the inseparable diastereomers 24a and 24b (85.4%) after 2 hours. Spectral data for the mixture (R_f 0.385, 20% EtOAc/hexanes): IR (CHCl₃) 3077, 2950, 2850,

2736, 2456, 1729, 1638, 1433, 1414, 1377, 1352, 1321, 1118, 1074, 1024, 989, 920, 869, 845, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.397 and 1.481 (3,s), 1.47-1.92 (6,m), 2.510 and 2.549 (1,bs), 2.514 and 2.578 (1,bs), 3.37-3.50 (1,m), 3.7044 (3,s), 3.87-3.99 (1,m), 4.73-4.77 and 4.77-4.82 (1,m), 5.05-5.09 (1,s), 5.10-5.15 (1,m), 5.69-5.90 (1,m); ^{13}C NMR (CDCl_3) δ 19.92 and 20.04 (CH_2), 20.70 and 22.24 (CH_3), 25.06 and 25.17 (CH_2), 31.16 (CH_2), 42.93 and 43.72 (CH_2), 51.77 (CH_2), 62.90 and 63.27 (CH_2), 78.73 and 80.12 (C), 94.83 and 95.88 (CH), 118.14 and 118.52 (CH_2), 132.64 (CH), 174.01 and 174.26 (C).

Methyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate (24a and 24b, Entry 3).

Alkylation of (S)-3a as in Entry 2 but with toluene as solvent afforded 24a and 24b in a 6 to 1 ratio in 36.8% yield after 6 hours. Due to the slow progress of the reaction at -78°C the reaction mixture was allowed to warm to -20°C over the first 5 hours of the reaction. Spectral data corresponded with the products from the reaction in THF.

Ethyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate (25a and 25b, Entry 4).

Alkylation of (S)-3b with 2.7 equivalents of allyl iodide afforded a 5 to 1 ratio of the inseparable diastereomers 25a and 25b (85.2%) after 2.5 hours. Spectral data for the

mixture (R_f 0.426, 20% EtOAc/hexanes): IR (CHCl_3) 3078, 3007, 2943, 2852, 1725, 1638, 1556, 1537, 1453, 1441, 1376, 1255, 1156, 1121, 1074, 1032, 990, 922, 869, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.273 and 1.280 (3,t, $J=7.1$ Hz), 1.388 and 1.479 (3,s), 1.48-1.93 (6,m), 2.49-2.60 (2,m), 3.37-3.50 (1,m), 3.89-3.99 (1,m), 4.10-4.30 (2,m), 4.72-4.82 (1,m), 5.05-5.17 (2,m), 5.70-5.93 (1,m); ^{13}C NMR (CDCl_3) δ 13.98 and 14.07 (CH_3), 19.95 and 20.04 (CH_2), 21.02 and 22.21 (CH_3), 25.12 and 25.21 (CH_2), 31.24 (CH_2), 42.77 and 43.98 (CH_2), 60.71 (CH_2), 62.89 and 63.22 (CH_2), 78.82 and 80.12 (C), 95.00 and 96.01 (CH), 118.11 and 118.46 (CH_2), 132.70 and 132.80 (CH), 173.57 and 173.83 (C).

Isopropyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate
(26a and 26b, Entry 5).

Alkylation of (S)-3c with 2.8 equivalents of allyl iodide afforded a 6 to 1 ratio of the inseparable diastereomers 26a and 26b (84.6%) after 1.25 hours. Spectral data for the mixture (R_f 0.511, 20% EtOAc/hexanes): IR (CHCl_3) 3077, 3015, 2980, 2943, 2851, 1720, 1638, 1465, 1453, 1440, 1374, 1352, 1257, 1159, 1102, 1073, 1031, 991, 920, 869, 847, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.2424 and 1.2536 (6,d, $J=6.3$ Hz), 1.3713 and 1.4677 (3,s), 1.46-1.95 (6,m), 2.46-2.52 (2,m) and 2.5637 (2,d, $J=7.3$ Hz), 3.37-3.47 (1,m), 3.90-3.99 (1,m), 4.71-4.74 and 4.75-4.79 (1,m), 5.020 (1,m, $J=6.3$ Hz), 5.07-5.16 (2,m), 5.72-5.91 (1,m); ^{13}C NMR (CDCl_3) δ 20.05 and 20.24 (CH_2), 21.39

(CH₃), 21.50 (CH₃), 21.60 (CH₃), 21.68 (CH₃), 22.22 (CH₃), 25.17 and 25.24 (CH₂), 31.31 and 31.40 (CH₂), 42.60 and 44.72 (CH₂), 62.97 and 63.42 (CH₂), 68.18 (CH), 79.00 and 80.21 (C), 95.35 and 96.23 (CH), 118.10 and 118.40 (CH₂), 132.75 and 132.96 (CH), 173.13 and 173.36 (C).

t-Butyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate
(27a/c and 27b/d, Entry 6).

Alkylation of (R/S)-3d with 3.2 equivalents of allyl iodide afforded a 4 to 1 mixture of the inseparable diastereomers 27a/c and 27b/d (92.3%) after 2 hours. Spectral data for the mixture (R_f 0.519, 20% EtOAc/hexanes): IR (CHCl₃) 3078, 3023, 3005, 2944, 2851, 1719, 1638, 1453, 1392, 1368, 1321, 1276, 1255, 1233, 1152, 1117, 1073, 1030, 991, 949, 921, 868, 847, 814 cm⁻¹; ¹H NMR (CDCl₃) δ 1.343 and 1.439 (3,s), 1.456 and 1.462 (9,s), 1.45-1.93 (6,m), 2.45-2.50 and 2.52-2.58 (2,m), 3.38-3.51 (1,m), 3.90-4.00 (1,m), 4.74-4.78 and 4.78-4.81 (1,m), 5.05-5.16 (2,m), 5.72-5.94 (1,m); ¹³C NMR (CDCl₃) δ 20.04 and 20.16 (CH₂), 21.60 and 22.31 (CH₃), 25.22 and 25.30 (CH₂), 27.83 and 27.95 (3CH₃), 31.40 and 31.50 (CH₂), 42.74 and 44.44 (CH₂), 62.89 and 63.24 (CH₂), 79.37 and 80.38 (C), 80.85 and 81.03 (C), 95.15 and 96.12 (CH), 117.94 and 118.24 (CH₂), 132.98 and 133.20 (CH), 172.69 and 173.01 (C).

Isopropyl 2-Methyl-2-O-tetrahydropyranylpent-4-enecarboxylate
(26a and 26b, Entry 7).

Alkylation of (S)-3c with 2.5 equivalents of allyl bromide afforded a 2 to 1 mixture of the inseparable diastereomers 26a and 26b (66.1%) after 6.5 hours. Spectral data were identical to those from the prior experiment (Entry 5).

Methyl 2-Methyl-3-phenyl-2-O-tetrahydropyranylpropanecarboxylate (28c and 28d, Entry 8).

Alkylation of (R)-3a with 2.7 equivalents of benzyl bromide afforded a 4 to 1 ratio of the separable diastereomers 28c and 28d in 93% yield. Spectral data for 28c (R_f 0.32): $[\alpha]_D^{26} = + 68.71^\circ$ (c 1.32, CHCl_3); IR (CHCl_3) 3009, 2948, 2851, 1729, 1602, 1494, 1453, 1379, 1353, 1323, 1273, 1201, 1117, 1074, 1033, 989, 946, 907, 869, 813 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 0.84-1.95 (6,M), 1.32 (3,s), 3.04 (1,d, $J=13.4$ Hz), 3.12 (1,d, $J=13.4$ Hz), 3.35-3.45 (1,m), 3.70 (3,s), 3.89-3.99 (1,m), 4.75-4.82 (1,m), 7.18-7.30 (5,m); $^{13}\text{C NMR}$ (CDCl_3) δ 19.08 (CH_2), 20.06 (CH_3), 25.13 (CH_2), 31.07 (CH_2), 45.26 (CH_2), 51.86 (CH_3), 63.33 (CH_2), 78.85 (C), 94.42 (CH), 126.55 (CH), 127.87 (CH), 130.52 (CH), 136.13 (C), 174.09 (C).

For 28d (R_f 0.35): $[\alpha]_D^{24} = + 54.2^\circ$ (c 1.84, CHCl_3); IR (CHCl_3) 3028, 3009, 2949, 2850, 1729, 1602, 1494, 1452, 1377, 1351, 1322, 1257, 1179, 1116, 1074, 1023, 991, 908, 869, 815

cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (3,s), 1.49-1.95 (6,m), 3.01 (1,d,J=13.5 Hz), 3.08 (1,d,J=13.5 Hz), 3.35-3.45 (1,m), 3.65 (3,s), 3.72-3.82 (1,m), 4.80 (1,dd,J=3.5,3.7 Hz), 7.20-7.29 (5,m); ¹³C NMR (CDCl₃) δ 19.60 (CH₃), 22.25 (CH₂), 25.35 (CH₂), 31.21 (CH₂), 46.09 (CH₂), 51.83 (CH₃), 62.32 (CH₂), 81.14 (C), 95.82 (CH), 126.58 (CH), 127.75 (CH), 130.58 (CH), 136.11 (C), 174.48 (C).

Methyl 2-Methyl-3-phenyl-2-O-tetrahydropyranyl-propanecarboxylate (28a and 28b, Entry 9).

Alkylation of (S)-3a in the presence of HMPA catalyst (462.8 mg, 2.583 mmol) with 2.2 equivalents of benzyl bromide afforded 28a (70.6%) and 28b (20.6%) after 45 minutes. Spectral data for 28a (R_f 0.32, 20% EtOAc/hexanes): [α]_D²⁴ = -64.0° (c 1.32, CHCl₃); IR (CHCl₃) 3009, 2948, 2851, 1730, 1602, 1494, 1353, 1273, 1115, 1074, 1033, 989, 946, 907, 869, 813 cm⁻¹; ¹H NMR (CDCl₃) δ 1.320 (3,s), 1.48-1.92 (6,m), 3.0423 (1,d,J=13.4 Hz), 3.1170 (1,d,J=13.4 Hz), 3.35-3.45 (1,m), 3.701 (3,s), 3.90-3.99 (1,m), 4.75-4.80 (1,m), 7.18-7.28 (5,m); ¹³C NMR (CDCl₃) δ 19.09 (CH₃), 20.06 (CH₂), 25.13 (CH₂), 31.07 (CH₂), 45.26 (CH₂), 51.86 (CH₃), 63.33 (CH₂), 78.85 (C), 94.42 (CH), 126.55 (CH), 127.87 (CH), 130.52 (CH), 136.13 (C), 174.09 (C).

For 28b (R_f 0.35): [α]_D²⁴ = -43.98° (c 4.90, CHCl₃); IR (CHCl₃) 3028, 3009, 2947, 2851, 1735, 1601, 1494, 1452, 1377,

1351, 1322, 1258, 1207, 1198, 1178, 1111, 1074, 1030, 991, 952, 908, 868, 815 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27-1.94 (6,M), 1.479 (3,s), 3.0104 (1,d,J=13.4 Hz), 3.0793 (1,d,J=13.4 Hz), 3.35-3.43 (1,m), 3.653 (3,s), 3.70-3.82 (1,m), 4.8043 (1,dd, J=3.5,3.8 Hz), 7.18-7.30 (5,m); ^{13}C NMR (CDCl_3) δ 19.62 (CH_2), 22.27 (CH_3), 25.36 (CH_2), 31.23 (CH_2), 46.11 (CH_2), 51.86 (CH_3), 62.35 (CH_2), 81.17 (C), 95.86 (CH), 126.61 (CH), 127.78 (CH), 130.61 (CH), 136.14 (C), 174.55 (C).

Methyl 2-Methyl-2-O-tetrahydropyranylpropanecarboxylate
(29a/c, Entry 10).

Alkylation of (R/S)-3a with 1.3 equivalents of iodomethane afforded 29a/c in 50% yield after 5 hours. The reaction progress was initially very slow so it was allowed to warm from -78°C to 0°C over the first 3 hours. Spectral data: IR (CHCl_3) 3022, 3005, 2947, 2851, 1727, 1465, 1453, 1434, 1383, 1363, 1276, 1230, 1153, 1074, 1030, 990, 952, 908, 869, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.39-1.95 (6,m), 1.452 (3,s), 1.497 (3,s), 3.39-3.49 (1,m), 3.717 (3,s), 3.89-3.97 (1,m), 4.70-4.74 (1,m); ^{13}C NMR (CDCl_3) δ 20.214 (CH_2), 24.952 (CH_2), 25.095 (CH_2), 25.388 (CH_3), 31.286 (CH_2), 51.884 (CH_3), 63.263 (CH_2), 77.178 (C), 95.821 (CH), 175.015 (C).

Methyl 2-Methyl-2-O-tetrahydropyranylundecanecarboxylate
(30a/c and 30b/d, Entry 11).

Alkylation of (R/S)-3a with 1.3 equivalents of 1-iodononane afforded 30a/c, 30b/d as the mixed diastereomers in 16% yield after 6 hours. The reaction was carried out at -40 to -50°C. Spectral data for the product mixture: ^1H NMR (CDCl_3) δ 0.877 (3,t,J=6.4 Hz), 1.20-1.85 (25,m), 3.35-3.50 (1,m), 3.697 and 3.708 (3,s), 3.88-3.97 (1,m), 4.67-4.71 and 4.73-4.77 (1,m); ^{13}C NMR (CDCl_3) δ 14.04 (CH_3), 20.25 (CH_2), 20.60 and 22.54 (CH_3), 22.61 (CH_2), 23.49 (CH_2), 25.18 and 25.28 (CH_2), 29.24 (CH_2), 29.39 (CH_2), 29.45 (CH_2), 29.69 and 29.78 (CH_2), 31.37 (CH_2), 31.83 (CH_2), 38.52 and 39.89 (CH_2), 51.82 (CH_3), 63.18 and 63.45 (CH_2), 79.27 and 80.61 (C), 94.71 and 96.24 (CH), 174.78 and 175.16 (C).

Methyl 2-Methyl-2-O-tetrahydropyranylundecanecarboxylate (30a/c and 30b/d, Entry 12).

Alkylation of (R/S)-3a with 1.2 equivalents of nonyl iodide in the presence of HMPA catalyst (1 equivalent) afforded 30a/c and 30b/d in 59% yield in a 3 to 2 ratio after 6 hours. The reaction was allowed to warm from -78°C to -40°C after 4 hours. Spectral data for the product mixture (30a/c R_f 0.49, 30b/d R_f 0.52, 20% EtOAc/hexanes): ^1H NMR (CDCl_3) δ 0.877 (3,t,J=6.4 Hz), 1.20-1.85 (25,m), 3.35-3.50 (1,m), 3.697 and 3.708 (3,s), 3.88-3.97 (1,m), 4.67-4.71 and 4.73-4.77 (1,m); ^{13}C NMR (CDCl_3) δ 14.04 (CH_3), 20.25 (CH_2), 20.60 (CH_3), 22.54 (CH_3), 22.61 (CH_2), 23.49 (CH_2), 25.18 (CH_2), 25.28 (CH_2),

29.24 (CH₂), 29.39 (CH₂), 29.45 (CH₂), 29.69 (CH₂), 29.78 (CH₂), 31.37 (CH₂), 31.83 (CH₂), 38.52 (CH₂), 39.89 (CH₂), 51.82 (CH₃), 63.18 (CH₂), 63.45 (CH₂), 79.27 (C), 80.61 (C), 94.71 (CH), 96.24 (CH), 174.78 (C), 175.16 (C).

5-Iodo-2-methyl-1-pentene.

4-Methyl-4-penten-1-yl p-toluenesulfonate (1.7 g, 6.68 mmol) was dissolved in 50 mL acetone in a 250 mL flask equipped with a stir bar under argon. Sodium iodide (10.04 g, 67 mmol) was added and the mixture stirred for 45 min. The reaction mixture was then warmed to 50°C for 1 min, at which time TLC showed no remaining tosylate. The mixture was diluted with water (250 mL) and extracted with ether (2 x 125 mL). The combined ether extracts were dried over MgSO₄, filtered, and the solvent removed in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with 10% ether/pentane to afford the iodide (1.4 g, quantitative) as a pale yellow oil. ¹H NMR (CDCl₃) δ 1.72 (3,s), 1.89-2.01 (2,m,J=7 Hz), 2.12 (2,t,J=7 Hz), 3.18 (2,t,J=7 Hz), 4.72 (1,bs), 4.76 (1,bs); ¹³C NMR (CDCl₃) δ 6.42 (CH₂), 22.26 (CH₃), 31.21 (CH₂), 38.23 (CH₂), 111.08 (CH₂), 143.69 (C).

Methyl 2,6-Dimethyl-2-O-tetrahydropyranylhept-6-enecarboxylate (31a and 31b, Entry 13).

Alkylation of (S)-3a with 1.1 equivalents of 5-iodo-2-

methyl-1-pentene in the presence of 2.4 equivalents of HMPA catalyst afforded a 2 to 1 ratio of 31a and 31b in 82.8% yield after 5.5 hours. Spectral data for 31b (R_f 0.46, 20% EtOAc/hexanes): $[\alpha]_D^{25}$ -65.38° (c 1.50, CHCl_3); IR (CHCl_3) 3072, 3026, 3007, 2944, 2868, 1735, 1645, 1453, 1376, 1351, 1257, 1173, 1118, 1074, 1030, 988, 947, 908, 893, 868, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.256-1.91 (10,m), 1.489 (3,s), 1.695 (3,s), 2.005 (2,t, $J=7.2$ Hz), 3.40-3.50 (1,m), 3.712 (3,s), 3.90-3.99 (1,m), 4.67-4.74 (3,m); ^{13}C NMR (CDCl_3) δ 20.20 (CH_2), 21.37 (CH_2), 22.16 (CH_3), 22.64 (CH_3), 25.30 (CH_2), 31.37 (CH_2), 37.62 (CH_2), 39.39 (CH_2), 51.87 (CH_3), 63.13 (CH_2), 80.49 (C), 96.20 (CH), 110.13 (CH_2), 145.34 (C), 175.10 (C).

For 31a (R_f 0.42): $[\alpha]_D^{24}$ -51.9° (c 3.575, CHCl_3); IR (CHCl_3) 3072, 3009, 2948, 2851, 1729, 1646, 1453, 1374, 1352, 1260, 1234, 1196, 1174, 1118, 1074, 1032, 990, 946, 908, 892, 869, 813 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.23-1.91 (10,m), 1.418 (3,s), 1.698 (3,s), 2.011 (2,t, $J=7.3$ Hz), 3.38-3.47 (1,m), 3.702 (3,s), 3.90-3.99 (1,m), 4.672 (1,bs), 4.701 (1,bs), 4.74-4.78 (1,m); ^{13}C NMR (CDCl_3) δ 20.16 (CH_2), 20.66 (CH_3), 21.30 (CH_2), 22.07 (CH_3), 25.10 (CH_2), 31.28 (CH_2), 37.71 (CH_2), 37.89 (CH_2), 51.80 (CH_3), 63.36 (CH_2), 79.09 (C), 94.68 (CH), 110.06 (CH_2), 145.23 (C), 174.61 (C).

Methyl 2,6-Dimethyl-2-O-tetrahydropyranylhept-6-enecarboxylate
(21c and 21d, Entry 14).

Alkylation of (R)-3a at 2 times normal scale with 1.2 equivalents of 5-iodo-2-methyl-1-pentene in the presence of 2.4 equivalents of HMPA catalyst afforded a 3 to 2 ratio of 21c and 21d in 83.8% yield after 9 hours. Spectral data for 21d (R_f 0.46, 20% EtOAc/hexanes): $[\alpha]_D^{25} +64.59^\circ$ (c 3.44, CHCl_3); IR (CHCl_3) 3072, 3028, 3007, 2947, 2870, 1731, 1649, 1453, 1376, 1351, 1257, 1173, 1118, 1074, 1030, 988, 947, 908, 892, 868, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.26-1.91 (10,m), 1.489 (3,s), 1.696 (3,s), 2.006 (2,t, $J=7.2$ Hz), 3.40-3.50 (1,m), 3.713 (3,s), 3.89-3.98 (1,m), 4.66-4.74 (3,m); ^{13}C NMR (CDCl_3) δ 20.19 (CH_2), 21.36 (CH_2), 22.15 (CH_3), 22.63 (CH_3), 25.30 (CH_2), 31.36 (CH_2), 37.62 (CH_2), 39.38 (CH_2), 51.86 (CH_3), 63.12 (CH_2), 80.49 (C), 96.20 (CH), 110.13 (CH_2), 145.34 (C), 175.10 (C).

For 21c (R_f 0.42): $[\alpha]_D^{25} +49.5^\circ$ (c 4.82, CHCl_3); IR (CHCl_3) 3072, 3009, 2949, 2851, 1729, 1649, 1453, 1374, 1352, 1260, 1234, 1196, 1174, 1118, 1074, 1032, 990, 891, 869, cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27-1.90 (10,m), 1.417 (3,s), 1.697 (3,s), 2.010 (2,t, $J=7.3$ Hz), 3.37-3.47 (1,m), 3.701 (3,s), 3.89-3.97 (1,m), 4.671 (1,bs), 4.700 (1,bs), 4.74-4.79 (1,m); ^{13}C NMR (CDCl_3) δ 20.20 (CH_2), 20.69 (CH_3), 21.34 (CH_2), 22.10 (CH_3), 25.14 (CH_2), 31.32 (CH_2), 37.75 (CH_2), 37.93 (CH_2), 51.84 (CH_3), 63.41 (CH_2), 79.15 (C), 94.73 (CH), 110.09 (CH_2), 145.29 (C), 174.67 (C).

Methyl 2,6-Dimethyl-2-O-tetrahydropyranylhept-6-enecarboxylate (31a/c and 31b/d, Entry 15).

Alkylation of (R/S)-3a with 5-iodo-2-methyl-1-pentene in toluene and without HMPA afforded 31a/c and 31b/d in a 4 to 1 ratio in 14.1% yield after 10.5 hours. Due to the very slow reaction progress the reaction was allowed to warm from -78°C to 0°C over the first 3 hours and was stirred at 0° for the remaining 7.5 hours. NMR spectral data matched the products from the alkylation done in THF (Entry 13).

Isopropyl 2,6-Dimethyl-2-O-tetrahydropyranylhept-6-enecarboxylate (32a/c and 32b/d, Entry 16).

Alkylation of (R/S)-3c with 1.1 equivalents of 5-iodo-2-methyl-1-pentene in the presence of 1.2 equivalents of HMPA catalyst afforded a 3 to 1 ratio of the inseparable diastereomers 32a/c and 32b/d in 46.4% yield after 4.5 hours. Spectral data for the mixture (R_f 0.477, 20% EtOAc/hexanes): ^1H NMR (CDCl_3) δ 1.251 (6,d,J=6.3 Hz), 1.39-1.90 (10,m), 1.3933 and 1.4729 (CH_3), 1.700 (CH_3), 2.005 (2,t,J=7.4 Hz), 3.36-3.48 (1,m), 3.89-3.99 (1,m), 4.670 (1,bs), 4.695 (1,bs), 4.80-4.87 (1,m), 4.97-5.09 (1,m,J=6.3 Hz); ^{13}C NMR (CDCl_3) δ 20.27 and 20.34 (CH_2), 21.26 (CH_3), 21.46 (CH_2), 21.54 (CH_3), 21.66 (CH_3), 22.18 (CH_3), 25.25 and 25.33 (CH_2), 31.42 and 31.54 (CH_2), 37.63 and 37.71 (CH_2), 37.94 and 39.81 (CH_2), 63.12 and 63.46 (CH_2), 68.06 and 68.15 (CH), 79.48 and 80.59 (C), 95.14 and

96.46 (CH), 110.02 (CH₂), 145.49 (C), 173.72 (C).

Methyl 2-Phenylmethyl-2-O-tetrahydropyranylpent-4-enecarboxylate (33a and 33b, Entry 17).

Alkylation of (S)-3e with 1.8 equivalents of allyl iodide afforded 33a and 33b in a 4 to 1 ratio and 60% yield after 2 hours. Spectral data for 13a (R_f 0.52, 20% EtOAc/hexanes): $[\alpha]_D^{26}$ -41.45 (\pm 2.75, CHCl₃); IR (CHCl₃) 3080, 3028, 3009, 2947, 2851, 1736, 1637, 1602, 1494, 1453, 1434, 1388, 1372, 1352, 1254, 1226, 1180, 1154, 1113, 1074, 1026, 981, 922, 869, 814 cm⁻¹; ¹H NMR (CDCl₃) δ 1.28-1.95 (6,m), 2.66-2.71 (2,m), 3.047 (2,s), 3.40-3.50 (1,m), 3.586 (3,s), 3.88-3.98 (1,m), 4.898 (1,dd,J=3 Hz, 5 Hz), 5.132-5.188 (2,m), 5.88-6.06 (1,m), 7.18-7.27 (5,m); ¹³C NMR (CDCl₃) δ 19.92 (CH₂), 25.25 (CH₂), 31.09 (CH₂), 39.57 (CH₂), 42.44 (CH₂), 51.56 (CH₃), 63.04 (CH₂), 83.38 (C), 95.82 (CH), 118.77 (CH₂), 126.47 (CH), 127.72 (2CH), 130.35 (2CH), 133.11 (CH), 136.25 (C), 173.25 (C).

For 13b (R_f 0.49): $[\alpha]_D^{26}$ -67.12° (\pm 0.76, CHCl₃); IR (CHCl₃) 3030, 3015, 3009, 2948, 2851, 1730, 1638, 1494, 1453, 1440, 1262, 1116, 1074, 1030, 977, 909, 869, 814 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26-1.92 (6,m), 2.45 (1,dd,J=6.9 Hz, 16.4 Hz), 2.675 (1,dd,J=7 Hz, 15.8 Hz), 3.195 (2,d,J=2.7 Hz), 3.39-3.48 (1,m), 3.685 (3,s), 3.92-4.01 (1,m), 4.90-4.94 (1,m), 5.09-5.21 (2,m), 5.77-5.93 (1,m), 7.20-7.30 (5,m); ¹³C NMR (CDCl₃) δ 20.12 (CH₂), 25.18 (CH₂), 31.10 (CH₂), 36.18 (CH₂), 41.36

(CH₂), 51.76 (CH₃), 63.47 (CH₂), 81.64 (C), 94.86 (CH), 118.72 (CH₂), 126.64 (CH), 128.05 (2CH), 130.43 (2CH), 132.72 (CH), 135.90 (C), 173.04 (C).

Methyl 2-Phenylmethyl-2-O-tetrahydropyranylpent-4-enecarboxylate (23c and 23d, Entry 18).

Alkylation of (R)-3e with 2 equivalents of allyl iodide afforded a 3 to 1 ratio of 13c and 13d in 50% yield after 3.5 hours. The diastereomers were not separated but the diastereomer ratio was determined by integration of the ¹H NMR spectrum. Spectral data for the mixture: ¹H NMR (CDCl₃) δ 1.26-1.92 (6,m), 2.40-2.50 and 2.61-2.72 (2,m), 3.048s and 3.194d (2, J=2.9 Hz), 3.40-3.50 (1,m), 3.587 and 3.679 (3,s), 3.89-4.00 (1,m), 4.89-4.93 (1,m), 5.09-5.21 (2,m), 5.78-6.06 (1,m), 7.18-7.28 (5,m); ¹³C NMR (CDCl₃) δ 19.92 and 20.06 (CH₂), 25.13 and 25.24 (CH₂), 31.09 (CH₂), 36.09 and 39.57 (CH₂), 41.30 and 42.42 (CH₂), 51.56 and 51.70 (CH₃), 63.06 and 63.41 (CH₂), 81.56 and 83.38 (C), 94.79 and 95.82 (CH), 118.68 and 118.78 (CH₂), [126.48, 126.59, 127.72, 127.99, 130.35, 132.67, and 133.10] (5CH), 135.84 and 136.25 (C), 172.98 and 173.25 (C).

Methyl 2-(2-Methylpropyl)-2-O-tetrahydropyranylpent-4-enecarboxylate (34a and 34b, Entry 19).

Alkylation of (S)-3f with 3 equivalents of allyl iodide

afforded equal amounts of 34a and 34b in 30% yield after 35 min. Spectral data for 34a (R_f 0.59, 20% EtOAc/ hexanes): $[\alpha]_D^{27}$ -51.96° (c 1.40, CHCl_3); IR (CHCl_3) 3076, 3028, 3007, 2951, 2868, 2359, 1735, 1637, 1465, 1452, 1435, 1386, 1367, 1352, 1257, 1157, 1119, 1073, 1029, 981, 920, 889, 869, 854, 814 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.845, 3,d,J=6.3 Hz), 0.924 (3,d,J=6.4 Hz), 1.25-1.90 (9,m), 2.55-2.74 (2,m), 3.40-3.50 (1,m), 3.704 (3,s), 3.90-3.99 (1,m), 4.81-4.85 (1,m), 5.05-5.15 (2,m), 5.78-5.95 (1,m); ^{13}C NMR (CDCl_3) δ 20.24 (CH_2), 23.69 (CH_3), 23.86 (CH_3), 24.02 (CH), 25.28 (CH_2), 31.34 (CH_2), 40.72 (CH_2), 45.27 (CH_2), 51.62 (CH_3), 63.32 (CH_2), 82.86 (C), 95.89 (CH), 118.28 (CH_2), 133.35 (CH), 174.48 (C).

For 34b (R_f 0.54): $[\alpha]_D^{27}$ -65.9° (c 1.34, CHCl_3); IR (CHCl_3) 3077, 3026, 3007, 2952, 2868, 1727, 1638, 1453, 1440, 1386, 1367, 1353, 1299, 1230, 1154, 1121, 1074, 1033, 981, 922, 869, 813 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.865 (3,d,J=6.4 Hz), 0.909 (3,d,J=6.3 Hz), 1.27-1.92 (9,m), 2.53-2.80 (2,m), 3.39-3.48 (1,m), 3.676 (3,s), 3.90-4.00 (1,m), 4.81-4.86 (1,m), 5.07-5.17 (2,m), 5.70-5.87 (1,m); ^{13}C NMR (CDCl_3) δ 20.07 (CH_2), 23.36 (CH_3), 23.71 (CH), 24.07 (CH_3), 25.19 (CH_2), 31.21 (CH_2), 37.60 (CH_2), 43.75 (CH_2), 51.63 (CH_3), 63.25 (CH_2), 81.18 (C), 94.20 (CH), 118.09 (CH_2), 133.02 (CH), 173.86 (C).

Methyl 2-(2-Methylpropyl)-2-O-tetrahydropyranylpent-4-enecarboxylate (24c and 24d, Entry 20).

Alkylation of (R)-3f with 1.5 equivalents of allyl iodide afforded a 4 to 5 ratio of 14c to 14d in 54% yield after 1.25 hours. The products were not separated but the diastereomer ratio was determined by integration of the ^1H NMR spectrum. Spectral data for the mixture: ^1H NMR (CDCl_3) δ 0.82-0.98 (6,m), 1.46-1.93 (9,m), 2.52-2.79 (2,m), 3.37-3.50 (1,m), 3.675 and 3.704 (3,s), 3.88-3.99 (1,m), 4.79-4.86 (1,m), 5.02-5.16 (2,m), 5.70-5.95 (1,m); ^{13}C NMR (CDCl_3) δ 20.01 and 20.17 (CH_2), [23.30, 23.65, 23.79, and 24.01] (2CH_3 and CH), 25.14 and 25.22 (CH_2), 31.16 and 31.27 (CH_2), 37.53 and 40.66 (CH_2), 43.68 and 45.21 (CH_2), 51.56 (CH_3), 63.18 and 63.23 (CH_2), 81.11 and 82.79 (C), 94.14 and 95.82 (CH), 118.04 and 118.21 (CH_2), 132.96 and 133.28 (CH), 173.80 and 174.39 (C).

2-(2-Propenyl)-2-O-tetrahydropyranylpantolactones (25a and 25b, Entry 21).

Alkylation of (S)-3g with 1.5 equivalents of allyl iodide afforded 25a and 25b in a 3 to 1 ratio in 30% yield after 21 hours. Spectral data for 25a (R_f 0.43, 20% EtOAc/hexanes): $[\alpha]_D^{27} +56.0$ (c 2.77, CHCl_3); IR (CHCl_3) 3077, 2945, 2869, 1766, 1638, 1465, 1452, 1440, 1431, 1392, 1363, 1323, 1259, 1176, 1139, 1073, 1032, 990, 971, 955, 936, 921, 870, 845, 821 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.086 (3,s), 1.168 (3,s), 1.42-1.90 (6,m),

2.280 (1,dd, J=9.5 Hz, 15.8 Hz), 2.961 (1,dm,J=15.8 Hz), 3.51-3.60 (1,m), 3.732 (1,d,J=8.0 Hz), 3.93-4.02 (1,m), 4.088 (1,d,J=8.0 Hz), 5.027 (1,d,J=4.8 Hz), 5.098-5.119 (1,m), 5.124-5.193 (1,dm,J=11.6 Hz), 5.961-6.126 (1,m); ^{13}C NMR (CDCl_3) δ 18.04 (CH_3), 19.81 (CH_2), 21.66 (CH_3), 25.04 (CH_2), 31.29 (CH_2), 33.89 (CH_2), 43.92 (C), 63.44 (CH_2), 77.43 (CH_2), 81.36 (C), 94.69 (CH), 117.67 (CH_2), 132.61 (CH), 175.57 (C).

For 25b (R_f 0.33): $[\alpha]_D^{27} +52.0^\circ$ (c 1.46, CHCl_3); ^1H NMR (CDCl_3) δ 1.078 (3,s), 1.153 (3,s), 1.49-1.90 (6,m), 2.24 (1,dd,J=8.8 Hz, 16.0 Hz), 2.86 (1,dm,J=16.0 Hz), 3.46-3.56 (1,m), 3.735 (1,d,J=8.1 Hz), 3.78-3.90 (1,m), 4.235 (1,d,J=8.1 Hz), 4.95-4.99 (1,m), 5.12-5.15 (1,m), 5.17 (1,d,J=9.6 Hz), 5.82-6.00 (1,m); ^{13}C NMR (CDCl_3) δ 17.90 (CH_3), 20.28 (CH_2), 22.51 (CH_3), 25.00 (CH_2), 31.08 (CH_2), 33.24 (CH_2), 44.21 (C), 63.76 (CH_2), 77.13 (CH_2), 79.35 (C), 94.26 (CH), 118.29 (CH_2), 131.82 (CH), 176.34 (C).

2-(2-Propenyl)-2-O-tetrahydropyranylpantolactones (25a and 25b, Entry 22).

Alkylation of (S)-3g with 2 equivalents of allyl iodide in the presence of 1 equivalent of HMPA afforded 25a and 25b in a 2 to 1 ratio in 37% yield after 2 hours. The HMPA was added immediately after the allyl iodide. Spectral data for 25a and for 25b were similar to those obtained for Entry 21.

Methyl 2-Phenyl-2-O-tetrahydropyranylpent-4-enecarboxylate
(26a and 26b, Entry 23).

Alkylation of (S)-3h (118.8 mg, 0.475 mmol) with 2 equivalents of allyl iodide afforded 26a (103.7 mg, 75.3%) and 26b (8.7 mg, 6.3%) after 2 hours. Spectral data for 26a (R_f 0.423, 20% EtOAc/hexanes): IR (CHCl_3) 3028, 3015, 2948, 2851, 1730, 1638, 1493, 1447, 1433, 1371, 1352, 1243, 1201, 1181, 1113, 1073, 1032, 960, 920, 908, 870, 822 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.25-2.03 (6,m), 2.40-2.52 (1,m), 3.00-3.04 (2,m), 3.691 (3,s), 3.93-4.03 (1,m), 4.812 (1,t, $J=3.7$ Hz), 4.86-4.89 (1,m), 4.934 (1,s), 5.49-5.67 (1,m), 7.20-7.47 (5,m); ^{13}C NMR (CDCl_3) δ 19.63 (CH_2), 25.15 (CH_2), 31.18 (CH_2), 41.89 (CH_2), 52.32 (CH_3), 63.01 (CH_2), 84.53 (C), 96.19 (CH), 118.26 (CH_2), 125.91 (CH), 127.40 (CH), 127.84 (CH), 132.40 (CH), 139.49 (C), 172.72 (C).

For 26b (R_f 0.382): ^1H NMR (CDCl_3) δ 1.25-2.03 (6,m), 3.00-3.04 (2,m), 2.40-2.52 (1,m), 3.644 (3,s), 3.93-4.03 (1,m), 4.812 (1,t, $J=3.7$ Hz), 4.86-4.89 (1,m), 4.934 (1,s), 5.49-5.67 (1,m), 7.20-7.47 (5,m); ^{13}C NMR (CDCl_3) δ 19.74 (CH_2), 25.21 (CH_2), 30.95 (CH_2), 39.27 (CH_2), 52.15 (CH_3), 63.13 (CH_2), 82.18 (C), 94.31 (CH), 118.35 (CH_2), 125.79 (CH), 127.67 (CH), 128.11 (CH), 132.48 (CH), 140.20 (C), 173.19 (C).

Methyl 2-Phenyl-2-O-tetrahydropyranylpropanecarboxylate (27a and 27b, Entry 24).

Alkylation of (S)-3h with 2 equivalents of iodomethane in

the presence of 2 equivalents of HMPA afforded 27a and 27b in a 5 to 1 ratio in 89% yield after 5 hours. The (S)-3h was added as a solution in 2 mL dry THF and the HMPA was added immediately after the iodomethane. Spectral data for 27a (R_f 0.41, 20% EtOAc/hexanes): $[\alpha]_D^{27} -85.5^\circ$ (c 4.80, CHCl_3); IR (CHCl_3) 3011, 2946, 2852, 1732, 1492, 1445, 1433, 1376, 1351, 1256, 1180, 1151, 1117, 1073, 1031, 1022, 985, 945, 898, 868, 821 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27-2.04 (6,m), 1.833 (3,s), 3.47-3.56 (1,m), 3.685 (3,s), 3.94-4.03 (1,m), 4.847 (1,t, $J=3.7$ Hz), 7.22-7.38 (3,m), 7.50-7.56 (2,m); ^{13}C NMR (CDCl_3) δ 19.64 (CH_2), 25.21 (CH_2), 25.45 (CH_3), 31.27 (CH_2), 52.30 (CH_3), 62.56 (CH_2), 82.15 (C), 96.26 (CH), 125.02 (2CH), 127.49 (CH), 128.08 (2CH), 142.22 (C), 173.57 (C).

For 27b (R_f 0.361): $[\alpha]_D^{27} -58.8^\circ$ (c 1.07, CHCl_3); IR (CHCl_3) 3026, 3009, 2948, 2851, 1729, 1493, 1446, 1377, 1352, 1269, 1182, 1125, 1073, 1034, 982, 942, 897, 869, 845, 815 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.26-2.02 (6,m), 1.822 (3,s), 3.35-3.44 (1,m), 3.666 (3,s), 3.91-4.00 (1,m), 4.794 (1,t, $J=4$ Hz), 7.24-7.38 (3,m), 7.43-7.51 (2,m); ^{13}C NMR (CDCl_3) δ 19.87 (CH_2), 23.20 (CH_3), 25.16 (CH_2), 31.21 (CH_2), 52.24 (CH_3), 63.02 (CH_2), 80.30 (C), 94.47 (CH), 125.52 (2CH), 127.67 (CH), 128.16 (2CH), 141.90 (C), 173.69 (C).

2,6-Dimethyl-2-O-tetrahydropyranylhept-6-ene-1-ol (42d).

Ester 31d (125.5 mg, 0.4642 mmol) was dissolved in dry

ether (10 mL) under argon and cooled to 0°C with stirring in an ice bath. Lithium aluminum hydride (20.0 mg, 0.527 mmol) was added in one portion and the reaction was allowed to warm to room temperature. After 30 min the reaction was quenched by the sequential addition of 20 uL H₂O, 20 uL 4M NaOH, and 60 uL H₂O. The solution was filtered through a Pasteur filter pipette and the solid rinsed with ether. The filtrate was concentrated in vacuo and chromatographed on silica gel (50g) eluted with 20% EtOAc/hexanes to afford 42d (102.4 mg, 91%) as a colorless oil. Spectral data (*R_f* 0.244, 20% EtOAc/hexanes): [α]_D²⁵ +54.5° (*c* 2.60, CHCl₃); IR (CHCl₃) 3450, 3009, 2947, 2865, 1730, 1649, 1463, 1440, 1376, 1199, 1176, 1127, 1073, 1023, 993, 943, 893, 807, 668 cm⁻¹; ¹H NMR (CDCl₃) δ 1.187 (3,s), 1.714 (3,s), 1.26-1.90 (10,m), 2.020 (2,t,J=6 Hz), 3.336 (1,dd,J=8.0 and 12.3 Hz), 3.46-3.57 (2,m), 3.704 (1,t,J=6.3 Hz), 3.97-4.05 (1,m), 4.63-4.68 (1,m), 4.68 (1,bs), 4.72 (1,bs); ¹³C NMR (CDCl₃) δ 20.95 (CH₂), 21.25 (CH₂), 22.19 (2CH₃), 25.00 (CH₂), 32.13 (CH₂), 33.28 (CH₂), 38.01 (CH₂), 64.74 (CH₂), 68.06 (CH₂), 79.56 (C), 94.18 (CH), 110.11 (CH₂), 145.35(C).

2,6-Dimethylhept-6-ene-1,2-diol ((R)-43).

Alcohol 42d was placed in a 100 mL flask with a stir bar under argon and cooled to 0°C in an ice bath. A solution which was 1% HCl, 9% H₂O, and 90% CH₃OH (1 mL) was added via

syringe and the reaction stirred for 2 hours. The solution was diluted with ether (30 mL), washed with sat NaHCO_3 (5 mL), and the ether layer separated, dried with MgSO_4 (3g), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on silica gel 60 (50g) eluted with 50% EtOAc/hexanes to afford (R)-43 (62.4 mg, 93.3%) as a pale yellow oil. Spectral data (R_f 0.17, 50% EtOAc/hexanes): $[\alpha]_D^{26} +2.4$ (c 3.11, CHCl_3); IR (CHCl_3) 3579, 3441, 3072, 2941, 1730, 1649, 1461, 1374, 1113, 1044, 893 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.152 (3,s), 1.43-1.52 (4,m), 1.713 (3,s), 1.99-2.05 (2,m), 2.9-3.3 (1,bs), 3.32-3.47 (3,m), 4.68 (1,bs), 4.71 (1,bs); ^{13}C NMR (CDCl_3) δ 21.56 (CH_2), 22.22 (CH_3), 22.91 (CH_3), 38.06 (2CH_2), 69.51 (CH_2), 73.00 (C), 109.99 (CH_2), 145.49 (C).

2,6-Dimethylhept-6-ene-1,2-diol ((S)-43).

LAH reduction and acid hydrolysis of 31c (as for 31d but without chromatographic purification of the alcohol 42c) afforded (S)-43 in 89.4% yield for the 2 steps. The product was identical with the (R)-43 obtained above but with opposite rotation. Similarly treated 31a gave (R)-43 while 31b gave (S)-43.

(S)-Frontalin (S-38).

Diol (S)-43 (106.0 mg, 0.67 mmol) was dissolved in 10 mL of dry methanol and cooled to -78°C . Ozone in oxygen was

bubbled through the solution until the blue color persisted and the excess ozone was then removed by bubbling oxygen through the solution until the blue color disappeared. Dimethyl sulfide (355 mg, 5.7 mmol) was then added and the reaction stirred for 30 min. The reaction mixture was then warmed to 0°C and stirred for an additional 1 hour. The dimethyl acetal was then hydrolyzed by addition of 0.1 mL of 10% HCl and the reaction stirred for 15 min. The reaction was quenched with saturated NaHCO₃ (5 mL), diluted with Et₂O (100 mL), and 50 mL of water added. The layers were separated and the aqueous phase acidified (pH 2), diluted with 50 mL Et₂O, and made basic with 20 mL saturated NaHCO₃. The layers were separated and the combined ether extracts were dried with anhydrous MgSO₄, filtered, and concentrated to 1 mL by distillation. The concentrate was chromatographed on silica gel (50 g) eluted with 20% Et₂O/pentane. Fractions containing the product were collected together and concentrated by distillation to 0.75 mL. The concentrate was purified by GLC (94°C column temperature gave a 7 min retention time) to afford the product (62.9 mg, 66.1%) as a colorless oil. Spectral data: $[\alpha]_D^{14}$ -50.3° (c 2.3, Et₂O); ¹H NMR (CDCl₃) δ 1.33 (3,s), 1.44 (3,s), 1.47-1.71 (5,m), 1.78-1.99 (1,m), 3.457 (1,dd,J=1.5,6.7 Hz), 3.92 (1,d,J=6.7 Hz).

(R)-Frontalin (R-38).

Diol (R)-43 was similarly treated to afford (R)-frontalin which had identical spectral characteristics but opposite rotation.

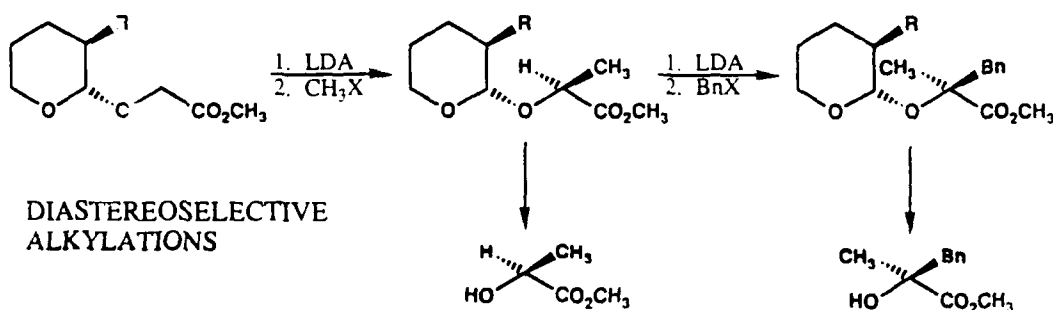
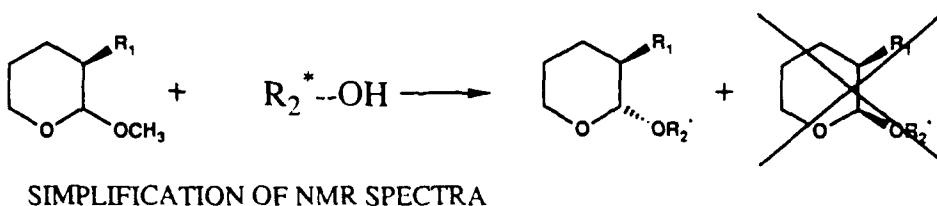
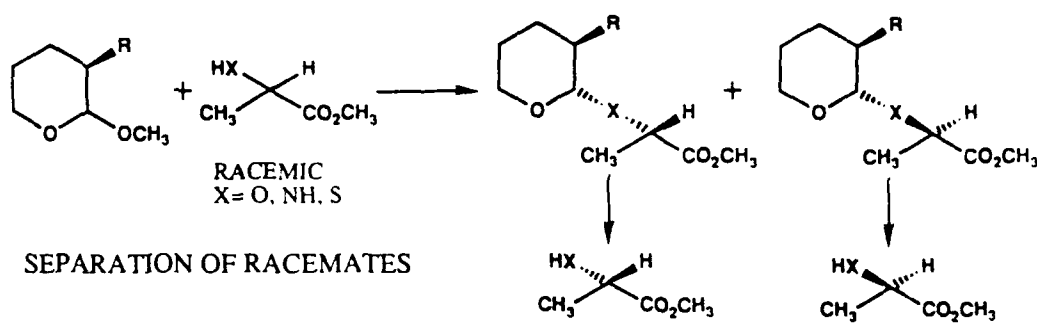
Methyl Atrolactate (44).

The pyranoside 27a (170.1 mg, 0.6435 mmol) was placed in a 5 mL flask with a stir bar under argon and cooled to 0°C. A solution (1 mL) which was 90% CH₃OH, 9% H₂O, and 1% HCl was added and the progress of the hydrolysis was monitored by TLC. After 1 hour the reaction was diluted with 20 mL diethyl ether, washed with 3 mL saturated sodium bicarbonate, and the aqueous phase extracted with an additional 10 mL of ether. The combined ether extracts were dried with MgSO₄ (2g), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 50g of silica gel 60 eluted with 5% EtOAc/hexanes to afford the alcohol (110.0 mg, 95%) as a colorless oil. Spectral data for the alcohol (*R_f* 0.32, 20% EtOAc/hexanes): $[\alpha]_D^{27} +4.92$ (≤ 2.84 , EtOH), $[\alpha]_D^{26} +54.5$ (≤ 2.84 , CHCl₃); IR (CHCl₃) 3497, 3059, 2982, 2951, 2844, 1953, 1885, 1729, 1598, 1582, 1493, 1445, 1372, 1259, 1151, 1071, 1028, 1001, 976, 940, 916, 872, 785, 733, 699, 658 cm⁻¹; ¹H NMR (CDCl₃) δ 1.780 (3,s), 3.756 (3,s), 3.823 (1,s), 7.25-7.39 (3,m), 7.52-7.56 (2,m); ¹³C NMR (CDCl₃) δ 26.60 (CH₃), 53.15 (CH₃), 75.70 (C), 125.08 (2CH), 127.73 (CH), 128.26 (2CH), 142.64 (C), 176.01 (C).

CHAPTER 3. DEVELOPMENT OF A "CHIRAL THP".

In Chapter 1 the synthesis of the THP and THF ethers of a variety of chiral α -hydroxyesters was discussed and the diversity of functionality which could be present either on the α -hydroxyester or on the THP or THF ring was highlighted. Also discussed was the observation that in four of the ring systems tested a second stereocenter on the ring could be linked to the chirality of the anomeric center. While this observation was an encouraging sign that diastereoselective reactions might be performed on the ring it also presented the possibility that established chirality at a linked center on the ring could direct the chirality of the anomeric center. Such a ring system would be in effect a "chiral THP (or THF)" which could see great utility in synthesis. Some examples are outlined in Scheme 39. First, a "chiral THP" might be used to resolve racemic mixtures of α -hydroxyesters (and possibly other α -hydroxycarbonyl compounds) by formation of a diastereomeric pair (due to the fixed chirality of the THP). Even racemic α -amino or α -mercapto carbonyls might be rendered separable by forming their "chiral THP" ethers. Second, a "chiral THP" might only form one diastereomer on addition of a chiral alcohol (instead of forming the two diastereomers that would normally be possible). This could greatly simplify purification and NMR spectra of THP-protected chiral alcohols.

Finally, diastereoselective alkylation (as demonstrated in Chapter 2) of a "chiral THP" could be used in the synthesis of chiral α -hydroxyesters (by alkylation of glycolates) or chiral α -alkyl- α -hydroxyesters.



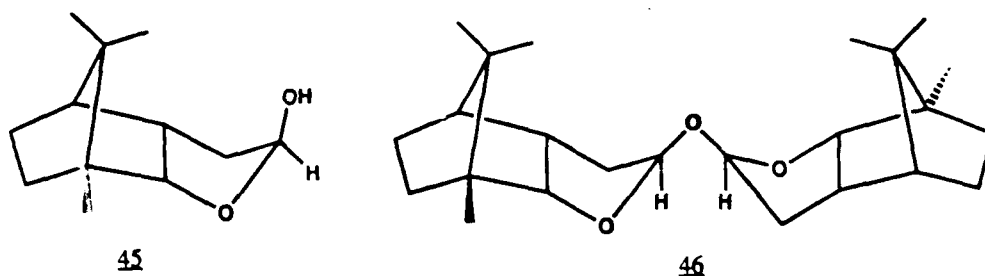
SCHEME 39: EXAMPLES OF THE SYNTHETIC UTILITY OF A CHIRAL THP

A. THE NOE-LACTOL

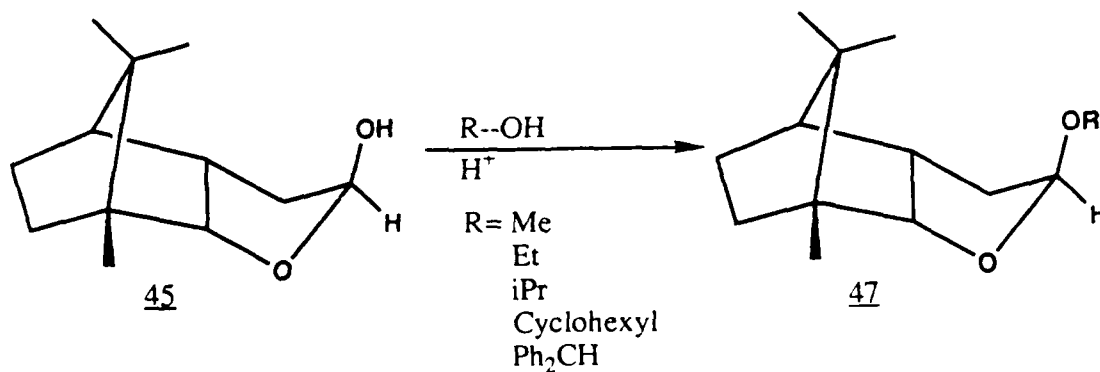
The only published research on a "chiral THP" (chiral lactol) was performed by Christian Noe and was published in a

series of papers⁵⁴⁻⁶³ from 1982 to 1989. A brief review of his work is presented here.

In his first paper in the series⁵⁴, Noe describes the synthesis of the lactol 45 starting from optically active camphor derivatives. The dimer 46 is now available from

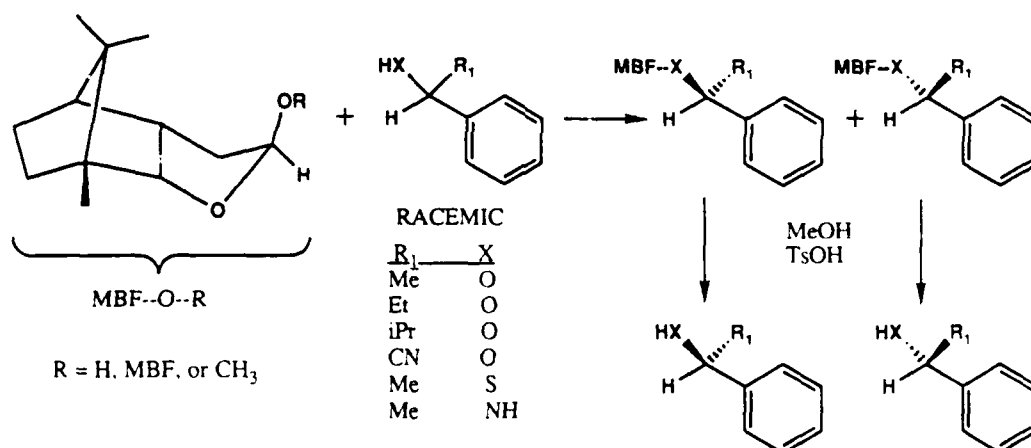


Aldrich Chemical Company for \$47/gram and its enantiomer is also available from Aldrich for \$69/gram. He also describes a series of experiments which demonstrated that transacetalization with alcohols yields the $\alpha(\text{exo})$ -acetals 47 with high diastereoselectivity (Scheme 40).



SCHEME 40: TRANSACETALIZATION OF THE NOE-LACTOL

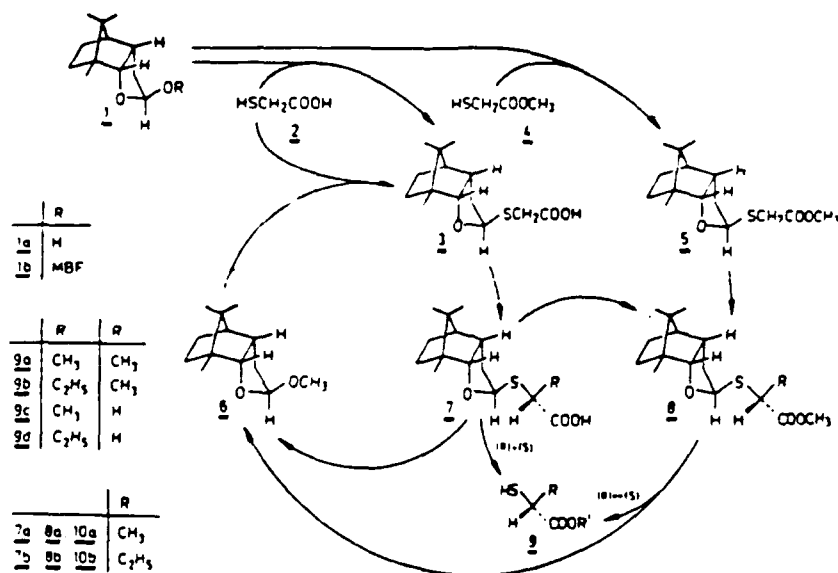
Noe's second paper⁵⁵ describes the use of either 45, 46, or the methyl lactol 47 to resolve racemic mixtures of chiral benzyl alcohols, thiols, and amines. As shown in Scheme 41, reaction of the lactol with a racemic benzyl alcohol, thiol, or amine (with acid catalysis) gave the lactol diastereomers shown which could be separated either by chromatography or by crystallization. Each of the resolved diastereomers could then be hydrolyzed in methanol with acid catalysis to reform 47 and free the enantiomerically pure compound.



SCHEME 41: NOE'S RESOLUTION OF CHIRAL ALCOHOLS

Noe's third paper⁵⁶ (briefly discussed in Chapter 2) demonstrated the use of lactol 46 in performing diastereoselective alkylations of mercaptoacetic acid (Scheme 42). Note that the alkylation gives predominantly the product with the (R)-stereochemistry when 46 is the starting material (the (S)-diastereomer was formed in only minor amounts and was

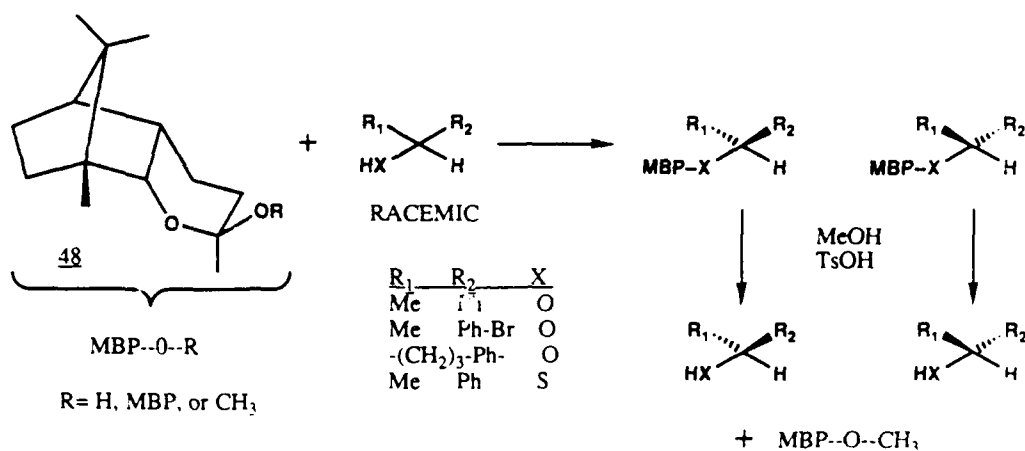
removed by chromatography). To produce the (S)-diastereomer one would simply use the enantiomer of 46 and go through the same reaction sequence.



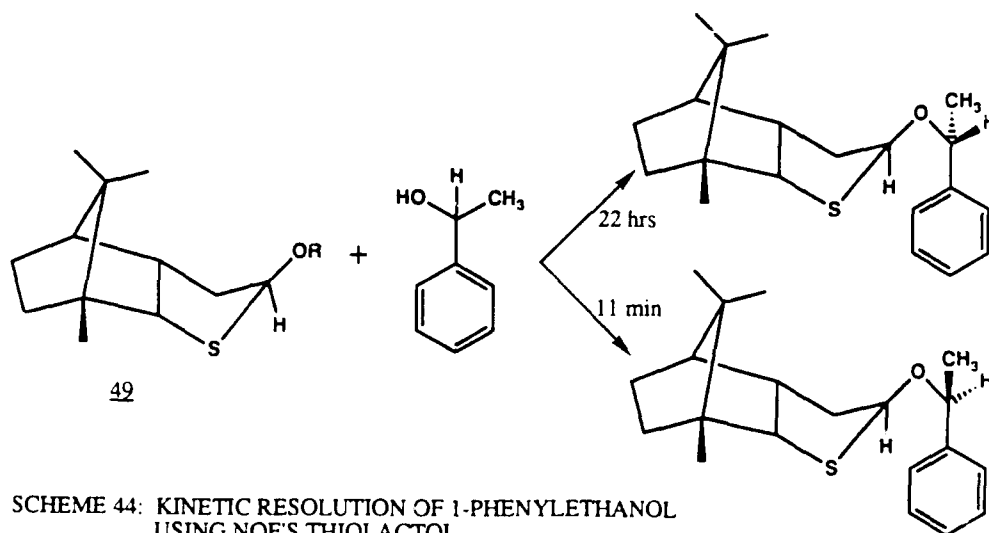
SCHEME 42: NOE'S ALKYLATION OF α -MERCAPTOACETIC ACID

In the fourth paper⁵⁷ in the series Noe describes the synthesis of the pyranoside homolog of furanolactols 45-47. Lactol 48 was also useful for resolving racemic mixtures of chiral alcohols and a thiol (Scheme 43).

Noe published a further modification to his chiral lactol⁵⁸ when he synthesized the thiolactol 49 and used it in the kinetic resolution of racemic 1-phenylethanol (Scheme 44).



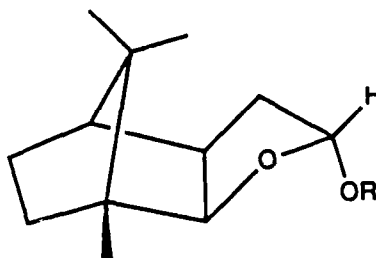
SCHEME 43: RESOLUTION OF ALCOHOLS WITH NOE'S PYRANOSIDE



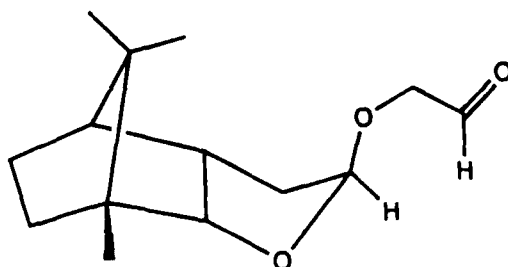
SCHEME 44: KINETIC RESOLUTION OF 1-PHENYLETHANOL USING NOE'S THIOLACTOL

The (S)-1-phenylethanol reacts more quickly with **49** to form the thioacetal but (R)-1-phenylethanol forms the more stable product thermodynamically. Thus by controlling the reaction conditions (especially reaction time) Noe was able to control which of the thioacetals was the predominant product.

In later papers Noe was able to: synthesize (S)-benzoin by selective binding of his lactol to the (S)-alcohol of meso-hydrobenzoin, followed by oxidation⁵⁹; give general rules for the determination of absolute conformation of chiral α -hydroxy-substituted nitriles, alkynes and aldehydes based on selective acetal formation and NMR chemical shifts of the acetals⁶⁰; demonstrate⁶¹ that the exo-lactol 50 underwent much of the same chemistry as the endo-lactol 45; describe the

50

synthesis of α -hydroxylactols and compare their reactivity to the reactivity of the unsubstituted lactols⁶³; and describe the results of doing aldol condensation reactions⁶² with the glycol aldehyde lactol 51.

51

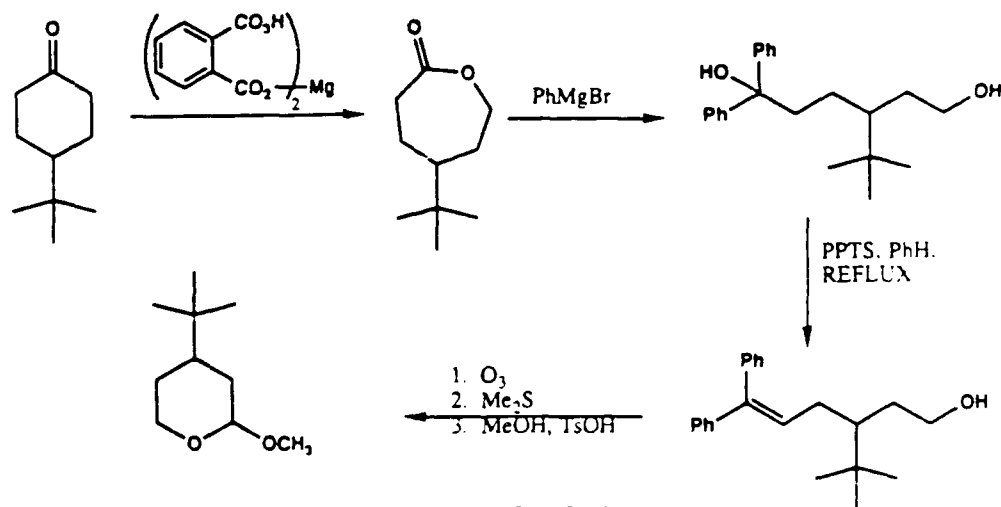
A few disadvantages to Noe's lactol present themselves. First, though the Noe-lactol is commercially available it is expensive (\$47/gram for the (+)-dimer, \$69/gram for the (-)-dimer). This cost disadvantage is mitigated somewhat in that the lactol is normally recovered in good yield as the methyl furanoside. Second, all the resolutions of chiral alcohols required that one of the groups on the alcohol be either planar or linear (aromatic ring, alkyne, nitrile, aldehyde, etc) while the other was not. Third, in the alkylation the diastereoselectivity was only moderate, giving 54-60% d.e. Finally, Noe's reliance on acid catalysis for both the attachment and removal of the auxillary may present a problem if acid-sensitive alcohols are used. Due to the nature of the acetalization reaction, however, this disadvantage may not be easily overcome.

B. INITIAL ATTEMPTS AT A "CHIRAL THP/THF".

Our observation of the linked stereocenters in the four THP and THF ethers already discussed indicates that the notion of a "chiral THP" was feasible with our simple ring systems. However, in each of these ethers the stereocenter that is linked is either too reactive (carbomethoxy) or too sensitive (bromine, TBDMS-ether) to allow for much chemistry to be performed on the molecules. Thus we undertook the development

of other THP/THF ethers which would demonstrate the linked chiral center but without the reactivity or sensitivity of the compounds already prepared.

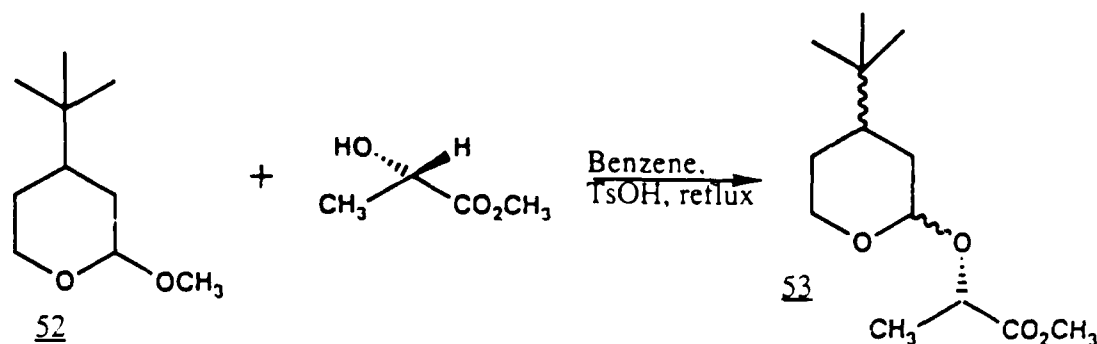
Our first attempt at developing a chiral THP was based on the notion of locking the THP ring in one conformation using a *t*-butyl "anchor" and then exploiting the anomeric effect to direct that the alcohol would have an axial orientation. Synthesis of the anchored pyranoside 52 was accomplished as shown in Scheme 45⁶⁴. Bayer-Villiger oxidation of 4-*t*-butyl-



SCHEME 45: SYNTHESIS OF AN ANCHORED PYRANOSIDE

cyclohexanone using magnesium monoperoxyphthalic acid gave the lactone quantitatively. The lactone was then alkylated with 2 equivalents of phenylmagnesium bromide to afford the diol which was subjected without purification to acid-catalyzed elimination to give the alkene in 72% yield for the 2 steps.

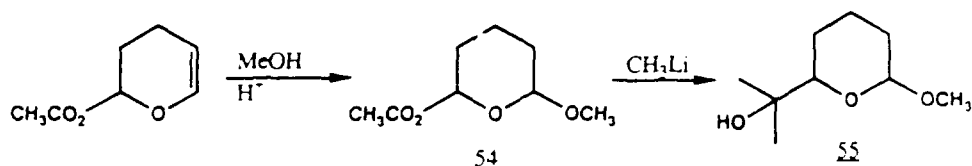
Ozonolysis followed by reductive workup and cyclization gave the methyl 4-*t*-butyltetrahydropyranosides 52 in moderate yield (49%). While the *t*-butyl group anchored the ring in one chair conformation it was apparent from the NMR that both axial (trans) and equatorial (cis) methoxy groups were present (in approximately a 4 to 1 ratio). Nevertheless transacetalization was attempted with (S)-methyl lactate in the hope that the larger lactate would increase the diastereoselectivity to give strictly the trans (axial) isomer. The exchange reaction (Scheme 46), however, gave all 4 of the possible lactate



SCHEME 46: *t*-BUTYL ANCHORED THP

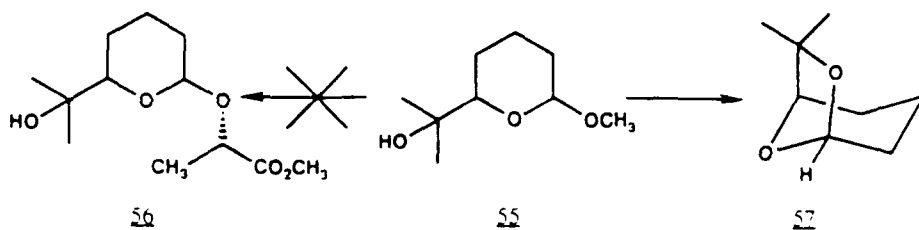
pyranosides 53 in approximately equal amounts. The most likely explanation is that bulkier groups are forced toward the cis (equatorial) conformation to reduce steric interactions.

Our second attempt was based more on electronic effects than on steric effects. As shown in Scheme 47, 6-carbomethoxy-2,3-dihydropyran was first converted to the methyl pyranoside 54. The trans:cis ratio was 5.2:1,

SCHEME 47. SYNTHESIS OF THE ALCOHOL 55

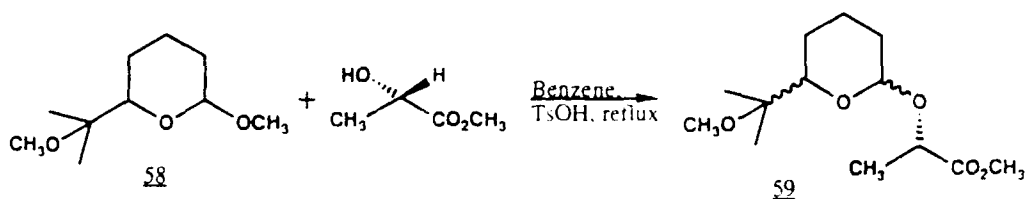
indicating that the carbomethoxy substituent does not always give complete diastereoselectivity in the addition of alcohols to the pyran. The ester was then alkylated with methyl lithium to form the alcohol 55. It was hoped that in the transacetalization reaction the alcohol appendage would coordinate to the intermediate carbocation and thus block the *cis* face from attack. As shown in Scheme 48, however, the alcohol added to the carbocation irreversibly to form the bicyclic compound 57 instead of promoting formation of the lactate pyranosides 56 as desired.

In order to allow coordination of the oxygen from the appendage to the intermediate carbocation but to prevent

SCHEME 48. CYCLIZATION OF ALCOHOL 55 TO THE BICYCLIC ACETAL

cyclization, the alcohol 55 was converted to its methyl ether 58. However, when the transacetalization reaction was attempted with 58 (Scheme 49) a mixture of all four possible

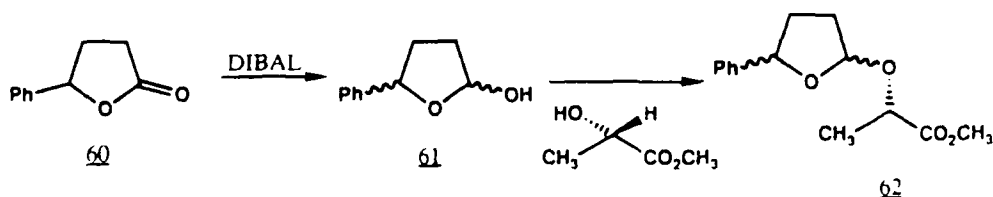
lactate pyranosides 59 was obtained.



SCHEME 49: TRANSACETALIZATION OF ETHER 58

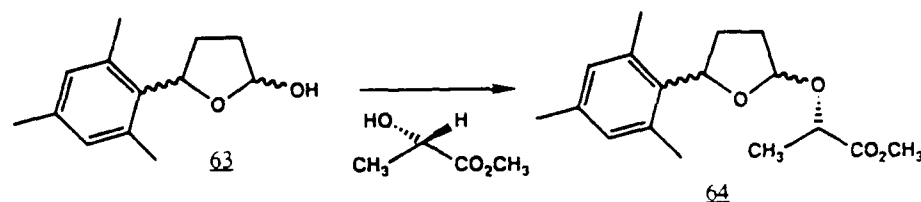
At this point we reconsidered the use of a THP ring system. It was apparent that the multitude of conformations that the THP ring could adopt would always serve to limit the diastereoselectivity we could achieve. We next considered the more conformationally restricted THF ring system. As before, our first approaches were based on steric interactions.

Our first attempt at a "chiral THF" was the 5-phenyl-THF ether 62. DIBAL reduction of the lactone 60 gave the lactol 61 which was then transacetalized with (S)-methyl lactate (Scheme 50) to give the ethers 62. Unfortunately, ^1H NMR of the product spots showed that all four products had been formed, albeit in a 4:1 ratio of trans:cis. We had achieved some diastereoselectivity but improvement was required.



SCHEME 50: ATTEMPT USING 5-PHENYL THF

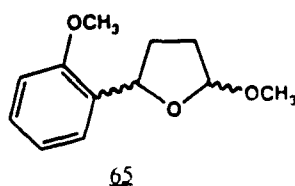
To increase the steric bulk and hopefully improve the diastereoselectivity the trimethylphenyl THF 63 was synthesized via a Grignard reaction between mesitaldehyde and 2-(2-bromoethyl)-1,3-dioxane followed by acid catalyzed cyclization. Transacetalization (Scheme 51) produced the



SCHEME 51: ATTEMPT USING 5-(2,4,6-TRIMETHYLPHENYL) THF

lactate furanosides 64 but ¹H NMR of one of the column fractions indicated that both of the trans furanosides were present (and were thus inseparable) and that some of the cis furanoside was also present. This indicated that using steric bulk alone would probably be insufficient to give complete diastereoselectivity in these systems. We next investigated stereoelectronic contributions in the THF system.

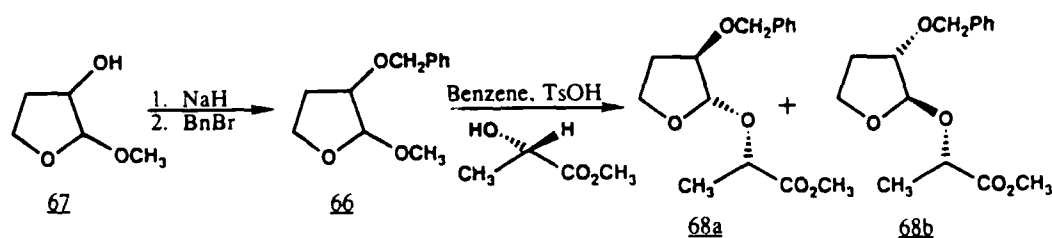
Our first attempt at using stereoelectronic effects in a THF system used the 2-methoxyphenyl THF 65 shown below.



However, 65 was synthesized as a roughly 1:1 mixture of the trans:cis methyl furanosides and offered little hope of giving the lactate furanosides diastereoselectively. It was thus abandoned in favor of the 3-benzyloxy THF 66 discussed below.

C. A "CHIRAL THF"

Our next attempt using stereoelectronic effects in a THF ring system was based on the diastereoselectivity shown by the TBDMS protected alcohol (Entry 16, Table 1). Though the TBDMS would probably be too sensitive to use in synthesis the same diastereoselectivity might be achieved using other protecting groups for the alcohol. Benzyl was the protecting group we chose to try. As shown in Scheme 52, the methyl 3-hydroxy-tetrahydrofuranoside 67 was deprotonated with NaH and reacted



SCHEME 52: SYNTHESIS OF (S)-METHYL LACTYL 3-BENZYLOXY THF ETHERS 68a AND 68b

with benzyl bromide to give the methyl 3-benzyloxytetrahydrofuranyl ethers 66 in 90% yield in a roughly 4:1 ratio of trans:cis. Transacetalization using (S)-methyl lactate in

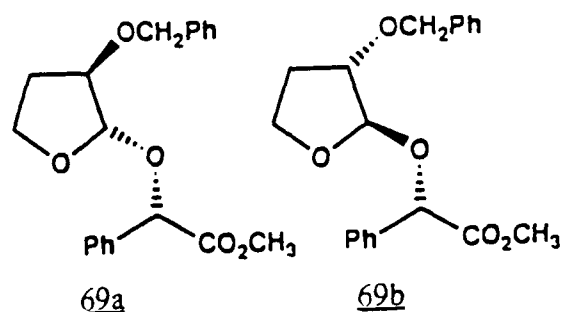
benzene with PPTS catalyst gave the trans lactate furanosides 68a and 68b in 39 and 37% yield respectively. The less polar diastereomer 68a is assumed to have the (2S, 3R) stereochemistry consistent with the other lactate pyranosides and furanosides. Likewise the more polar diastereomer 68b is assumed to have the (2R, 3S) stereochemistry. None of the products with the cis benzyloxy and lactate appendages were observed. The specific rotations of 68a and 68b were found to be -82.31° and $+5.56^\circ$ respectively. Subsequent reactions which also produced 68a gave material which had specific rotations ranging from -82.4° to -73.09° while reactions that produced 68b gave material which had specific rotations ranging from $+6.94^\circ$ to -1.3° . Possible sources of error include incomplete separation of the diastereomers, contamination of the products with other materials (either optically active or non-optically active), and epimerization of any of the chiral centers either during the reaction or during isolation or characterization.

The resolved lactate furanosides 68a and 68b were each subjected to acid catalyzed hydrolysis in methanol to generate the optically active ("chiral THF") methyl furanosides (R-66) and (S-66) in approximately 80% yield for the trans furanosides. The cis methyl furanosides could also be recovered in 10% yield though they were not used in the subsequent reactions (to keep from complicating the TLC's). The specific rotation for (R-66) (derived from 68a with rotation -74.3°)

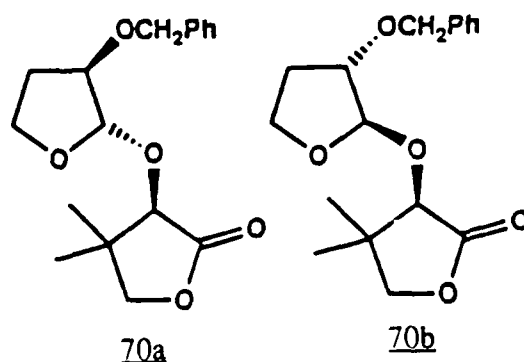
was -59.0° while the specific rotation for (S-66) (derived from 68b with rotation $+2.98^\circ$) was $+53.06^\circ$. Samples of (S-66) were then refluxed for 2.5 hours in methanol with PPTS and with TsOH to evaluate the potential for acid-catalyzed epimerization. The samples of (S-66) recovered from these reactions had specific rotations of $+61.7^\circ$ and $+64.4^\circ$ respectively. This increase in specific rotation (which may be due to better purity of the material) indicates that the methyl furanosides are not especially sensitive to acid-catalyzed epimerization of the 3-benzyloxy chiral center.

Reattachment of (S)-methyl lactate to the (R-66) obtained above using TsOH in benzene regenerated 68a in 74% yield. The specific rotation was -82.4° . A small amount (3%) of 68b was also isolated from the reaction indicating that either the initial separation of the diastereomers was incomplete or that some epimerization had occurred during either the hydrolysis reaction or during the reattachment of the lactate.

(S)-Methyl lactate was not the only α -hydroxy ester to gives separable diastereomers for the 3-benzyloxy tetrahydrofuranoside. A reaction of (S)-methyl mandelate with 66 gave the readily separable (α 1.30 in 20% EtOAc/hexanes) diastereomers 69a and 69b, one of which (69a) was crystalline.

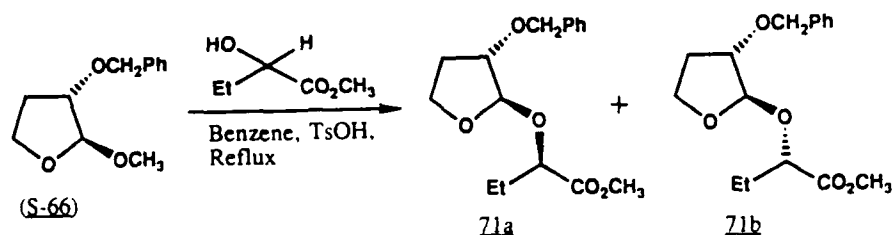


Purification of these diastereomers might thus also be done via recrystallization. In like manner (R)-pantolactone gave the separable diastereomers (α 1.33 in 20% EtOAc/hexanes) 70a and 70b.



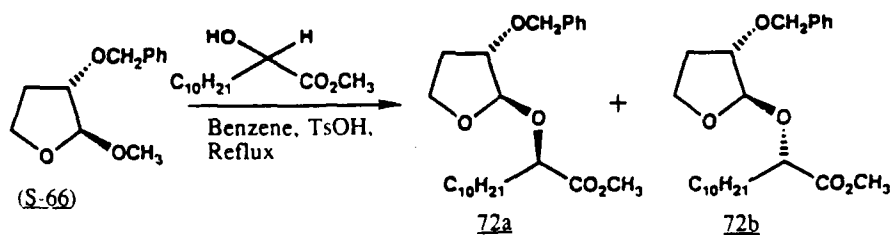
With the "chiral THF's" (R-66) and (S-66) in hand the next step was to test their utility in synthesis. We decided to investigate their ability to resolve racemic mixtures of several α -hydroxy esters and an α -mercapto ester. The fact that we obtained separable diastereomers using racemic methyl 2-benzyloxytetrahydrofuran 66 with (S)-methyl lactate indicates that using racemic methyl lactate with either (R-66) or (S-66) would also give separable diastereomers. In like

manner, reaction of (S-66) with racemic methyl α -hydroxybutanoate did give the separable diastereomers 71a and 71b (Scheme 53) while its reaction with racemic methyl α -hydroxy-



SCHEME 53: RESOLUTION OF RACEMIC METHYL α -HYDROXYBUTYRATE

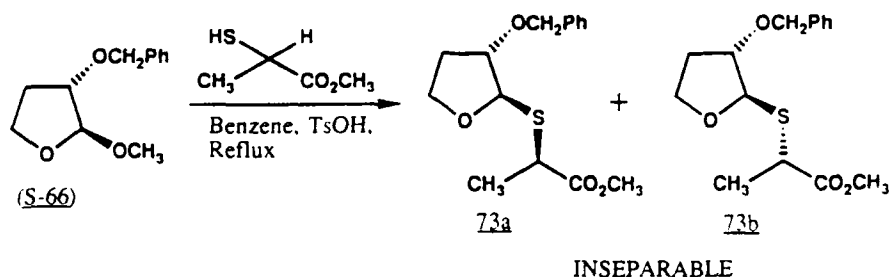
dodecanoate yielded the separable diastereomers 72a and 72b (Scheme 54). It is also of interest that the separability was



SCHEME 54: RESOLUTION OF RACEMIC METHYL α -HYDROXYDODECANOATE

essentially independent of the α -hydroxyester used since the α values were approximately 1.25 in 20% EtOAc/hexanes and 1.50 in 10% for each. An attempt to use this "chiral THF" to resolve racemic methyl thiolactate (Scheme 55) failed due to inseparability of the thiolactate furanosides 73a and 73b.

To demonstrate a completed resolution of one of the α -hydroxyesters the dodecanoate furanosides 72a and 72b were each subjected to TsOH-catalyzed hydrolysis in methanol to



SCHEME 55: ATTEMPTED RESOLUTION OF RACEMIC METHYL THIOLACTATE

give the recovered (S-66) and the free chiral α -hydroxyester. Thus 72a afforded (-)-methyl α -hydroxydodecanoate in 89% yield with a specific rotation of -7.06° while 72b afforded the (+)-isomer in 90% yield with a specific rotation of $+7.77^\circ$. A comprehensive search of the chemical abstracts and of Beilstein both manually and by computer indicated that neither of these enantiomers had been prepared before. The utility of this "chiral THF" is thus demonstrated.

Summary:

The "chiral THF's" (R-66) and (S-66) may be useful in organic syntheses, especially for the resolution of racemic mixtures of α -hydroxyesters. However, due to the large variations in specific rotations for (R-66), (S-66), and their lactate furanosides this project will require more research. Areas which ought to be investigated further include effects of temperature and catalyst concentration on the rate of decomposition of the furanosides and the use of other

catalysts to effect the transacetalizations. In addition, other approaches to chiral THP's or THF's which do not rely on an appendage adjacent to the anomeric center ought to be considered.

Methyl 4-t-Butyltetrahydropyranoside (52).

1,1-Diphenyl-4-t-butyl-hex-1-ene-6-ol (578.6 mg, 1.876 mmol) was dissolved in 50 mL dry methanol and cooled to -78°C . Ozone was added until the blue color persisted and the excess was removed by bubbling O_2 through the solution. Dimethyl sulfide (264.5 mg, 4.257 mmol), trimethyl orthoformate (4.5 mL, 41.0 mmol), and TsOH (53 mg, 0.28 mmol) were added sequentially and the reaction was allowed to warm to room temperature. The reaction was stirred for 24 hrs, the excess dimethyl sulfide oxidized with bleach (20 mL), and the solution diluted with diethyl ether (180 mL). The layers were separated and the aqueous phase was extracted twice with diethyl ether (25 mL each) and the combined ether phases were washed with water (20 mL), dried (MgSO_4), filtered, and the solvents removed in vacuo. The concentrate was chromatographed twice on silica gel 60 (50g) eluted with 2% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$. Only those fractions containing no benzophenone or other impurities were collected from the second column to afford 159.2 mg (49%) of the mixed products 52 (2 spots by TLC) as a yellow oil. This product mixture was used directly in the lactate exchange reaction. Spectral data for the mixture: ^1H NMR (CDCl_3) δ 0.83 and 0.85 (9,s), 1.09 -1.87 (5,m), 3.34 and 3.48 (3,s), 3.60-3.79 (2,m), 4.03-4.26 and 4.75-4.76 (1,m); ^{13}C NMR (CDCl_3) δ 26.36 and 26.60 (CH_2), 26.69 and 26.98 (3 CH_3), 31.15 and 32.83 (CH_2), 31.69 (C), 38.65 and 44.57 (CH), 54.34 and 56.00 (CH_3), 59.86

and 65.53 (CH₂), 98.61 and 103.55 (CH).

(S)-Methyl Lactyl 4-t-Butyltetrahydropyranyl Ether (53).

The methyl 4-t-butyltetrahydropyranoside diastereomers 52 (159.2 mg, 0.9241 mmol), (S)-methyl lactate (200 mg, 1.921 mmol), and PPTS (200 mg, 0.80 mmol) were dissolved in CH₂Cl₂ (40 mL) and heated to reflux for 28 hours. The CH₃OH/CH₂Cl₂ azeotrope was removed via a Dean-Stark trap and the solvent was replaced with dry CH₂Cl₂. The reaction was then cooled to room temperature, diluted with CH₂Cl₂ (100 mL), washed with saturated NaHCO₃ (10 mL), dried (MgSO₄), filtered, and the volatiles removed in vacuo. The concentrate was chromatographed on silica gel 60 eluted with 10% EtOAc/hexanes to afford three product spots at R_f's 0.44 (48.1 mg, 21%), 0.41 (100.4 mg, 44%), and 0.33 (21.3 mg, 9%). NMR spectra of the products 53 indicated that the spot at R_f 0.44 had the lactate appendage axial, the spot at R_f 0.33 had the lactate equatorial, and the spot with R_f 0.41 consisted of two products: one with the lactate axial and the other with it equatorial. Spectral data for the less polar spot, R_f 0.44: ¹H NMR (CDCl₃) δ 0.845 (9,s), 1.25-1.90 (5,m), 1.447 (3,d,J=7.0 Hz), 3.61-3.80 (2,m), 3.729 (3,s), 4.381 (1,q,J=7.0 Hz), 4.95-4.97 (1,m).

For the intermediate spot, R_f 0.41: ¹H NMR (CDCl₃) δ 0.842 and 0.864 (9,s), 1.20-2.00 (5,m), 1.39 and 1.45

(3,d,J=6.8 Hz, 7.0 Hz), 3.30-4.25 (2,m), 3.73 and 3.75 (3,s), 4.17 and 4.54 (1,q,J=6.8 Hz, 7.0 Hz), 4.38-4.44 and 4.93-4.98 (1,m,J=large, fine).

For the more polar spot, R_f 0.33: ^1H NMR (CDCl_3) δ 0.852 (9,s), 1.25-1.90 (5,m), 1.28 (3,d,J=7.0 Hz), 3.30-3.43 (1,m), 3.74 (3,s), 3.99-4.07 (1,m), 4.26 (1,q,J=7.0 Hz), 4.39-4.45 (1,m).

Methyl 6-Carbomethoxytetrahydropyranyl Ether (54).

6-Carbomethoxy-2,3-dihydropyran (3.0243 g, 21.275 mmol) was dissolved in dry CH_3OH (2 mL) and PPTS (51.4 mg, 0.205 mmol) was added. After stirring for 1 hour TLC showed no reaction progress so TsOH (3.9 mg, 0.02 mmol) was added; TsOH was also added at 3 hours (6.0 mg, 0.03 mmol) and 6 hours (10 mg, 0.05 mmol) and CH_3OH (10 mL) was added at 6 hours. The reaction was stirred overnight and then diluted with diethyl ether (75 mL), washed with sat NaHCO_3 (15 mL), and the layers separated. The aqueous phase was extracted with three 25 mL portions of diethyl ether and the combined ether extracts were dried (MgSO_4), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 75g silica gel 60 eluted with 20% EtOAc/hexanes to afford a 5.2:1 ratio of the trans and cis pyranosides 54 (3.5799g, 96.6%) as a colorless oil homogeneous by TLC (R_f 0.24, 20% EtOAc/hexanes). ^1H NMR of the mixture (CDCl_3) δ 1.50-2.02 (6,m), 3.40 and 3.51 (3,s), 3.77

(3,s), 4.1 and 4.85-4.89 (1,mult and broad singlet), 4.39 (1,dd,J=2.5Hz, 11.4 Hz).

Methyl 6-(1-Hydroxy-1-methylethyl)tetrahydropyranyl Ether (55).

Methyl lithium (10.0 mL of 1.4M, 14 mmol) in diethyl ether was dissolved in 10 mL dry diethyl ether and cooled to -78°C under argon. Methyl 6-carbomethoxytetrahydropyranyl ether 54 (1.1091 g, 6.367 mmol) in 10 mL dry ether was added dropwise over 10 minutes and the reaction was stirred for 1 hour. The reaction was quenched at -78°C with half-saturated NH₄Cl (10 mL) and diluted with diethyl ether (50 mL). The layers were separated and the aqueous phase extracted with an additional 25 mL ether. The combined ether extracts were dried (MgSO₄), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 100g silica gel 60 eluted with 10/20 % EtOAc/hexanes to afford 99.3 mg of mixed ketone (intermediate) with starting material and 1.0441 g (83.5%) of the product alcohols 55 (trans R_f 0.19, cis R_f 0.14; 20% EtOAc/hexanes). Spectral data for the mixture: ¹H NMR (CDCl₃) δ 1.16 and 1.181 (3,s), 1.21 and 1.24 (3,s), 1.30-1.90 (6,m), 2.46 and 2.57 (1,bs), 3.36 and 3.50 (3,s), 3.50-3.78 (1,m), 4.35 (1,dd,J=1.8 Hz, 9.3 Hz) and 4.77 (1,d,J=2.2 Hz); ¹³C NMR (CDCl₃) δ 17.78 and 21.89 (CH₂), 24.11 and 24.30 (CH₃), 24.42 and 24.83 (CH₂), 26.06 and 26.12 (CH₃), 29.45 and 30.86 (CH₂), 54.36 and 55.92

(CH₃), 65.74 and 71.68 (C), 74.61 and 82.38 (CH), 98.64 and 103.68 (CH).

Attempted Synthesis of (S)-Methyl Lactyl 6-(1-Hydroxy-1-methylethyl)tetrahydropyranyl Ether (56).

Methyl 6-(1-hydroxy-1-methylethyl)tetrahydropyranyl ether 55 (463.8 mg, 2.662 mmol) was dissolved in 50 mL of benzene in a 100 mL flask equipped with a stir bar and Dean-Stark trap under argon. (S)-Methyl lactate (540.5 mg, 5.192 mmol) and PPTS (81.8 mg, 0.33 mmol) were added and the reaction was refluxed for 2 hours. The reaction was then cooled to room temperature, quenched with saturated NaHCO₃ (10 mL), diluted with diethyl ether (50 mL), and the ether phase dried (MgSO₄), filtered, and the volatiles removed in vacuo. The concentrate was chromatographed on 50g silica gel 60 eluted with 10% EtOAc/hexanes to afford 159.2 mg (42%) of the bicyclic product 57 (R_f 0.49, 20% EtOAc/hexanes) resulting from attack of the tertiary alcohol appendage on the anomeric center. The product was volatile and had a pungent odor similar to pinene. ¹H NMR (CDCl₃) δ 1.264 (3,s), 1.429 (3,s), 1.50-2.14 (6,m), 3.82-3.87 (1,bs), 5.498 (1,bs); ¹³C NMR (CDCl₃) δ 15.48 (CH₂), 20.39 (CH₃), 24.82 (CH₂), 28.78 (CH₃), 30.06 (CH₂), 79.25 (CH), 80.21 (C), 101.73 (CH).

Methyl 6-(1-Methoxy-1-methylethyl)tetrahydropyranyl Ether
(58).

Sodium hydride (70.3 mg, 2.93 mmol) was dissolved in dry THF (25 mL) and methyl 6-(1-hydroxy-1-methylethyl)tetrahydropyranyl ether 55 (432.6 mg, 2.48 mmol) in 10 mL dry THF was slowly added via syringe. Iodomethane (390 mg, 2.75 mmol) was added via syringe and the reaction was stirred at room temperature for 2 hours. Since no reaction progress was noted by TLC the reaction mixture was heated to reflux for 2 hours at which time no starting material remained. The reaction was quenched with water (10 mL) and diluted with 50 mL ether. The layers were separated and the aqueous phase extracted with an additional 25 mL ether. The combined ether extracts were dried (MgSO_4), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 50g of silica gel 60 eluted with 10% EtOAc/hexanes to afford 392.2 mg (84%) of the mixed isomers 58 as a colorless oil. Spectral data for the mixture (R_f 's 0.42 and 0.39, 20% EtOAc/hexanes): ^1H NMR (CDCl_3) δ 1.169 (3,s), 1.178 (3,s), 1.215 (3,s), 1.20-1.93 (6,m), 3.4 (1,dd, $J=1.8$ Hz) and 3.61 (1,dd, $J=1.9$ Hz, 11.5 Hz), 3.253 and 3.476 (3,s), 3.361 and 3.363 (3,s), 4.274 (1,dd, $J=1.9$ Hz, 9 Hz) and 4.764 (1,bs); ^{13}C NMR (CDCl_3) δ 18.13 and 22.10 (CH_2), 20.33 and 20.46 (CH_3), 21.89 and 22.78 (CH_3), 24.25 and 24.56 (CH_2), 29.60 and 31.06 (CH_2), 49.50 and 49.59 (CH_3), 54.39 and 55.74 (CH_3), 73.43 and 81.38 (CH), 75.96 and

76.07 (C), 98.76 and 103.84 (CH).

(S)-Methyl Lactyl 6-(1-Methoxy-1-methylethyl)tetrahydro-pyranyl Ethers (59).

Methyl 6-(1-methoxy-1-methylethyl)tetrahydropyranyl ether 58 (197.1 mg, 1.047 mmol) was placed with (S)-methyl lactate (193.5 mg, 1.86 mmol), benzene (30 mL), and PPTS (50 mg) in a flame-dried flask equipped with a stir bar and Dean-Stark trap under argon. The mixture was refluxed for 2.5 hours and then cooled to room temperature, diluted with ether (75 mL), quenched with saturated NaHCO_3 (10 mL), and the layers separated. The ether phase was dried (MgSO_4), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 60g of silica gel 60 eluted with 20% EtOAc/hexanes. The products 59, 4 spots with R_f 's 0.32, 0.28, 0.26, and 0.21 by TLC (20% EtOAc/hexanes), were collected together to give 243.9 mg (89%) of a pale yellow oil. ^1H NMR (CDCl_3) indicated that all 4 possible products had formed. Proton chemical shifts for the hydrogen at the anomeric center and for the methoxy groups (respectively): product 1 (R_f 0.32): 4.169 (q, $J=6.9$ Hz), 3.747 (s), and 3.213 (s); product 2 (R_f 0.28): 4.511 (q, $J=7.0$ Hz), 3.732 (s), and 3.326 (s); product 3 (R_f 0.26): 4.318 (q, $J=6.8$ Hz), 3.744 (s), and 3.217 (s); product 4 (R_f 0.21): 3.607 (dd, $J=2.1$ Hz, 11.6 Hz), 3.730 (s), and 3.242 (s).

(S)-Methyl Lactyl 5-Phenyltetrahydrofuranyl Ethers (62).

γ -Phenyl- γ -butyrolactone 60 (497.3 mg, 3.066 mmol) was dissolved in methylene chloride (10 mL) and cooled to -78°C under argon. DIBAL (3.4 mL of 1M, 3.4 mmol) in methylene chloride was added via syringe and the reaction was stirred at -78°C for 2 hours. The reaction was then warmed to 0°C and 10% HCl (30 mL) was added. The mixture was shaken in a separatory funnel until both layers were clear. The layers were then separated and the organic phase dried (MgSO_4), filtered, and the solvent removed in vacuo. The concentrate was dissolved in benzene (100 mL) in a 250 mL flask equipped with a stir bar and Dean-Stark trap. (S)-Methyl lactate (690 mg, 6.63 mmol) and PPTS (50 mg) were added and the mixture was refluxed for 1 hour. Since TLC showed no remaining alcohol 61 the reaction was cooled to room temperature, quenched with saturated NaHCO_3 (10 mL), diluted with benzene (50 mL), and the layers separated. The organic phase was dried (MgSO_4), filtered, and the volatiles removed in vacuo. The concentrate was chromatographed on 125 g silica gel 60 eluted with 10% EtOAc/hexanes to afford 412.4 mg (54%) of a less polar spot (R_f 0.38, 20% EtOAc/hexanes) and 97.1 mg (13%) of a more polar spot (R_f 0.29) along with mixed fractions (not collected). ^1H NMR (CDCl_3) indicated that both product spots had 2 components, thus all 4 possible products 62 had been formed and the trans:cis ratio was approximately 4:1. ^1H chemical shifts for

the methoxy groups: Less polar spot: 3.734 (s) and 3.644 (s); more polar spot: 3.733 (s) and 3.582 (s).

Methyl 5-(2,4,6-Trimethylphenyl)tetrahydrofuran-3-yl Ethers (63).

Magnesium (209.7 mg, 8.63 mmol) was placed in 20 mL dry THF in a flame dried 100 mL flask equipped with a stir bar, addition funnel, and reflux condenser under argon. A solution of 2-(2-bromoethyl)-1,3-dioxane (1.465 g, 7.511 mmol) in 20 mL dry THF was added over 20 minutes after the reaction was initiated by warming to reflux. After the addition was complete the reaction was heated to reflux for an additional 15 minutes and then cooled to 35°C. A solution of mesitaldehyde (1.1665 g, 7.871 mmol) in 10 mL dry THF was then added and the reaction was refluxed overnight. The reaction was cooled to room temperature, quenched with 20 mL saturated NH_4Cl , diluted with 100 mL ether and 10 mL water, and the layers separated. The organic phase was dried (MgSO_4), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 100 g silica gel 60 eluted with 20% EtOAc/hexanes to afford 1.413 g (71%) of the product alcohol (R_f 0.38, 50% EtOAc/hexanes). A portion of the alcohol (466.6 mg, 1.765 mmol) was dissolved in 5 mL methanol and PPTS (50 mg) and TsOH (20 mg) were added over 4 hours. The reaction was then stirred overnight, diluted with ether (100 mL), quenched with saturated NaHCO_3 (10 mL), the layers separated, and the ether phase dried

(MgSO₄), filtered, and the solvent removed in vacuo. The concentrate was chromatographed on 50 g silica gel 60 eluted with 15% EtOAc/hexanes to afford the mixed product spots 63 (R_f's 0.72 and 0.67, 20% EtOAc/hexanes; 349.1 mg (89.8%) combined yield) as a colorless oil. ¹H NMR (CDCl₃) δ 2.232 (3,s), 1.80-2.3 (4,m), 2.333 and 2.407 (6,s), 3.274 and 3.372 (3,s), 5.10 and 5.21 (1,m), 5.30 and 5.43 (1,m), 6.791 and 6.808 (2,s); ¹³C NMR (CDCl₃) δ 20.45 (2CH₃), 20.63 (CH₃), 28.98 (CH₂), 32.96 (CH₂), 54.50 (CH₃), 75.59 (CH), 105.05 (CH), 129.99 (2CH), 133.11 (C), 136.34 (2C), 136.61 (C).

(S)-Methyl Lactyl 5-(2,4,6-Trimethylphenyl)tetrahydrofuranyl Ethers (64).

Methyl 5-(2,4,6-trimethylphenyl)tetrahydrofuranyl ether 63 (349.1 mg, 1.585 mmol) was dissolved in 25 mL benzene in a flask equipped with a stir bar and a Dean-Stark trap. (S)-Methyl lactate (219 mg, 2.10 mmol) and PPTS (50 mg) were added and the mixture was heated to reflux. After 3 hours additional PPTS (100 mg) and (S)-methyl lactate (400 mg) were added to try to force the reaction to products. After refluxing for 4 hours the reaction was cooled to room temperature and stirred overnight. The reaction was then diluted with 50 mL ether, quenched with saturated NaHCO₃ (10 mL), and the layers separated. The ether phase was dried (MgSO₄), filtered, and the volatiles removed in vacuo. The

concentrate was chromatographed on 50 g of silica gel 60 eluted with 15% EtOAc/hexanes. ^1H NMR of one of the column fractions indicated that both of the trans isomers were present--thus the lactate diastereomers 64 were deemed to be inseparable. A small amount of the cis isomer also was present in the NMR sample. The remaining product was not collected.

Methyl 5-(2-Methoxyphenyl)tetrahydrofuranyl Ether (65).

This material was prepared in a manner analagous to the methyl 5-(2,4,6-trimethylphenyl)THF ether 63 described above using o-anisaldehyde as the aldehyde for the Grignard reaction. The product spots (R_f 's 0.47 and 0.37, 20% EtOAc/hexanes) were each collected as colorless oils. Spectral data for the less polar diastereomer: ^1H NMR (CDCl_3) δ 1.58-1.71 (1,m), 1.89-2.15 (2,m), 2.39-2.57 (1,m), 3.404 (3,s), 3.812 (3,s), 5.25 (1,dd, $J=1.5$ Hz, 5.1 Hz), 5.39 (1,t, $J=7.0$ Hz), 6.83-7.41 (4,m); ^{13}C NMR (CDCl_3) δ 31.01 (CH_2), 32.00 (CH_2), 54.65 (CH_3), 55.21 (CH_3), 74.59 (CH), 105.23 (CH), 110.06 (CH), 120.37 (CH), 125.64 (CH), 127.91 (CH), 131.23 (C), 156.10 (C).

For the more polar diastereomer: ^1H NMR (CDCl_3) δ 1.72-1.92 (1,m), 2.01-2.10 (2,m), 2.30-2.45 (1,m), 3.49 (3,s), 3.80 (3,s), 5.11 (1,t, $J=3.0$ Hz), 5.40 (1,dd, $J=6.3$ Hz, 12.8 Hz), 6.8-7.6 (4,m); ^{13}C NMR (CDCl_3) δ 31.35 (CH_2), 33.57 (CH_2), 55.00 (CH_3), 55.24 (CH_3), 77.00 (CH), 105.41 (CH), 109.93 (CH),

120.67 (CH), 126.29 (CH), 127.87 (CH), 131.72 (C), 156.16 (C).

Methyl 3-Benzyloxytetrahydrofuranyl Ether (66).

Sodium hydride (299 mg, 12.5 mmol) was placed in 10 mL dry THF and cooled to 0°C under argon. Methyl-3-hydroxytetrahydrofuranyl ether 67 (synthesized as in Chapter 1, 1.1732 g, 9.9312 mmol) in 10 mL of dry THF was slowly added via syringe and the solution was allowed to warm to room temperature. The reaction was then again immersed in an ice bath and benzyl bromide (1.9063 g, 11.15 mmol) was added via syringe. The reaction was allowed to warm to room temperature and was stirred for 48 hours. The reaction was then diluted with ether (100 mL), washed with saturated NaHCO₃ (25 mL), and the ether phase dried (MgSO₄), filtered, and volatiles removed in vacuo. The concentrate was chromatographed on 55 g of silica gel 60 eluted with 20% EtOAc/hexanes to afford 1.8635 g (90.1%) of the mixed trans/cis products 66 (R_f's 0.33 and 0.20, respectively) as a pale yellow oil. The ratio of trans to cis products was estimated to be 4 to 1.

(S)-Methyl Lactyl 3-Benzyloxytetrahydrofuranyl Ethers (68a) and (68b).

The mixed methyl 3-benzyloxytetrahydrofuranyl ethers 66 (1.1166 g, 5.3617 mmol) were dissolved in 20 mL benzene and (S)-methyl lactate (2.0108 g, 19 mmol) and PPTS (205.5 mg)

were added. The reaction was refluxed for 5 days (with periodic removal of the benzene/methanol azeotrope) and went to approximately 75% completion. TsOH (65.8 mg) was then added and the reaction refluxed overnight. The reaction was then cooled to room temperature, diluted with 75 mL ether, and quenched with saturated NaHCO_3 (15 mL). The layers were separated and the ether phase was dried (MgSO_4), filtered, and the volatiles removed in vacuo. The concentrate was chromatographed 5 times on 60 g silica gel 60 eluted with 10/20% EtOAc/hexanes to afford the product diastereomers (less polar diastereomer 68a 590.5 mg, 39%; more polar diastereomer 68b 562.8 mg, 37%) as very pale yellow oils. Spectral data for 68a (R_f 0.33, 20% EtOAc/hexanes): $[\alpha]_D^{26} -82.31^\circ$ (c 5.37, CHCl_3); IR (CHCl_3) cm^{-1} 3022, 3009, 2953, 2898, 1742, 1495, 1453, 1435, 1372, 1276, 1145, 1110, 1080, 1021, 961, 913, 833; ^1H NMR (CDCl_3) δ 1.38 (3,d, $J=7.0$ Hz), 1.90-2.02 (1,m), 2.17-2.30 (1,m), 3.73 (3,s), 3.89-3.99 (1,m), 4.05-4.14 (2,m), 4.37 (1,q, $J=7.0$ Hz), 4.54 (1,d, $J=11.9$ Hz), 4.62 (1,d, $J=11.9$ Hz), 5.22 (1,s), 7.25-7.38 (5,m); ^{13}C NMR (CDCl_3) δ 18.75 (CH_3), 30.16 (CH_2), 51.83 (CH_3), 66.84 (CH_2), 69.66 (CH), 71.38 (CH_2), 82.85 (CH), 104.46 (CH), 127.56 (CH), 127.62 (CH), 128.28 (CH), 137.83 (C), 173.38 (C).

For 68b (R_f 0.27): $[\alpha]_D^{26} +5.56^\circ$ (c 5.82, CHCl_3); IR (CHCl_3) cm^{-1} 3017, 2952, 1745, 1600, 1495, 1453, 1435, 1371, 1353, 1281, 1143, 1107, 1046, 1027, 981, 914; ^1H NMR (CDCl_3)

δ 1.36 (3,d,J=6.8 Hz), 1.90-2.02 (1,m), 2.21-2.35 (1,m), 3.70 (3,s), 3.89-4.17 (4,m), 4.54 (2,s), 5.13 (1,s), 7.25-7.40 (5,m); ^{13}C NMR (CDCl_3) δ 18.15 (CH_3), 30.18 (CH_2), 51.76 (CH_3), 67.18 (CH_2), 71.41 (CH_2), 71.62 (CH), 83.03 (CH), 105.71 (CH), 127.58 (CH), 127.63 (CH), 128.32 (CH), 137.75 (C), 173.86 (C). Other runs of this reaction afforded products with similar R_f 's, IR, ^1H NMR, and ^{13}C NMR but with the following specific rotation values:

68a: $[\alpha]_D^{26} -82.4^\circ$ (\underline{c} 3.54, CHCl_3), $[\alpha]_D^{26} -79.57^\circ$ (\underline{c} 5.58, CHCl_3), $[\alpha]_D^{26} -74.3^\circ$ (\underline{c} 4.07, CHCl_3), $[\alpha]_D^{25} -73.93^\circ$ (\underline{c} 5.74, CHCl_3), $[\alpha]_D^{25} -73.09^\circ$ (\underline{c} 5.11, CHCl_3).

68b: $[\alpha]_D^{25} +6.94^\circ$ (\underline{c} 4.96, CHCl_3), $[\alpha]_D^{25} +4.18^\circ$ (\underline{c} 4.93, CHCl_3), $[\alpha]_D^{27} +2.98^\circ$ (\underline{c} 4.50, CHCl_3), $[\alpha]_D^{26} -1.3^\circ$ (\underline{c} 5.23, CHCl_3).

Methyl 3-(R)-Benzyloxytetrahydrofuranyl Ether (R-66).

The (S)-methyl lactyl 3-benzyloxytetrahydrofuranyl ether 68a (186.1 mg, 0.6639 mmol) was dissolved in 5 mL methanol and 59 mg of TsOH was added. The reaction was heated to reflux for 2.5 hours and then cooled to room temperature and stirred overnight. The reaction was then quenched with saturated NaHCO_3 (10 mL), diluted with 100 mL ether and 10 mL water, the layers separated, and the ether phase dried (MgSO_4), filtered, and volatiles removed in vacuo. The concentrate was chromatographed on 50 g of silica gel 60 eluted with 10/20% EtOAc/hexanes to afford 114.1 mg (82.5%) of the trans product

(R-66) and 12.6 mg (9.1%) of the cis product (91.6% combined yield) as colorless oils. Spectral data for (R-66) (R_f 0.33, 20% EtOAc/hexanes): $[\alpha]_D^{26}$ -59.0° (c 3.71, CHCl_3), ^1H NMR (CDCl_3) δ 1.89-2.01 (1,m), 2.10-2.23 (1,m), 3.318 (3,s), 3.89-4.12 (3,m), 4.533 (2,s), 4.948 (1,s), 7.23-7.36 (5,m); ^{13}C NMR (CDCl_3) δ 30.13 (CH_2), 54.31 (CH_3), 66.43 (CH_2), 71.33 (CH_2), 82.85 (CH), 106.86 (CH), 127.58 (CH), 128.30 (CH), 137.80 (C).

For the cis product (R_f 0.20): ^1H NMR (CDCl_3) δ 1.97-2.22 (2,m), 3.411 (3,s), 3.82 (1,q, $J=8.1$ Hz), 3.92-4.08 (2,m), 4.613 (2,s), 4.765 (1,d, $J=4.1$ Hz), 7.29-7.42 (5,m); ^{13}C NMR (CDCl_3) δ 28.01 (CH_2), 54.65 (CH_3), 64.56 (CH_2), 72.38 (CH_2), 78.52 (CH), 100.79 (CH), 127.79 (CH), 128.02 (CH), 128.35 (CH), 137.76 (C).

Methyl 3-(S)-Benzyloxytetrahydrofuranyl Ether (S-66).

The (S)-methyl lactyl 3-benzyloxytetrahydrofuranyl ether 68b (175.5 mg, 0.6261 mmol) was dissolved in 10 mL methanol with PPTS (172 mg) and the reaction mixture was heated to reflux for 19 hours. After workup and chromatography (as for the (R)-ether above) the trans methyl furanoside (S-66) (109.2 mg, 83.7%) was recovered as a yellow oil. No attempt was made to recover the cis product. The ^1H and ^{13}C NMR spectra were similar to the product recovered above but the specific rotation was $[\alpha]_D^{27}$ $+53.06^\circ$ (c 3.42, CHCl_3).

A repeat of this reaction (272.7 mg THF ether, 5 mL methanol,

35.7 mg TsOH, 3 hours reflux) afforded 110.0 mg (54%) of (S-66) ($[\alpha]_D^{25} +52.92^\circ$, c 3.10 CHCl_3) and 15.2 mg of the cis furanoside.

Methyl 3-(S)-Benzyloxytetrahydrofuranyl Ether (S-66).

The trans methyl furanoside prepared above (50.9 mg, 0.244 mmol) was refluxed in 5 mL of methanol with 15 mg PPTS (0.06 mmol, 25 mol%) for 2.5 hours. After workup and chromatography the trans methyl furanoside was recovered (35.4 mg, 69.5%) with specific rotation $[\alpha]_D^{28} +61.7^\circ$ (c 1.77, CHCl_3).

A parallel run using 58.3 mg (0.280 mmol) of the trans methyl furanoside, 5 mL methanol, and 2.3 mg TsOH (0.012 mmol, 4.3 mol%) gave 41.6 mg (71.4%) of the recovered trans methyl furanoside with specific rotation $[\alpha]_D^{27} +64.4^\circ$ (c 2.08, CHCl_3).

(S)-Methyl Lactyl (2S,3R)-3-Benzyloxytetrahydrofuranyl Ether (68a).

Methyl 3-(R)-benzyloxytetrahydrofuranyl ether (R-56) (114.0 mg, 0.547 mmol) was dissolved in 15 mL benzene with (S)-methyl lactate (167.0 mg, 1.604 mmol) and TsOH (26 mg). The reaction was heated to reflux under argon and the methanol/benzene azeotrope was removed via a Dean-Stark trap. After 1.25 hours the reaction was cooled to room temperature, diluted with ether (75 mL), and quenched with saturated NaHCO_3 (10 mL). The layers were separated and the ether phase was dried (MgSO_4), filtered, and the volatiles removed in vacuo. The

concentrate was chromatographed twice on 50 g of silica gel 60 eluted with 20% EtOAc/hexanes to afford 115.3 mg (75.2%) of 68a and approximately 4 mg (3%) of 68b. The NMR spectra for 68a were similar to the prior spectra but the specific rotation was $[\alpha]_D^{26} -82.4^\circ$ (c 3.54, CHCl_3). The ^1H NMR spectrum of the 68b was also similar to the prior spectrum.

(S)-Methyl Mandelyl 3-Benzoyloxytetrahydrofuranyl Ethers (69a) and (69b).

Racemic methyl 3-benzoyloxytetrahydrofuranyl ether 66 (315.4 mg, 1.514 mmol), (S)-methyl mandelate (271.3 mg, 1.633 mmol), and TsOH (32.0 mg, 0.168 mmol) were dissolved in 15 mL of benzene in a flask equipped with a stir bar and a Dean-Stark trap. The reaction was heated to reflux for 2.5 hours and then cooled to room temperature, diluted with ether (100 mL), and quenched with saturated NaHCO_3 (10 mL). The layers were separated and the ether phase was dried (MgSO_4), filtered, and the volatiles removed in vacuo. The concentrate was chromatographed twice on 50 g of silica gel 60 eluted with 10/20% EtOAc/hexanes and once with 50% ether/hexanes to afford 177.1 mg (34.2%) of the mandelate furanosides 69a and 69b (approximately equal amounts of each diastereomer). Spectral data for the less polar diastereomer 68a (R_f 0.30, 20% EtOAc/hexanes): mp $70.0-72.0^\circ\text{C}$; $[\alpha]_D^{29} -16^\circ$ (c 4.60, CHCl_3); IR (CHCl_3) cm^{-1} 3064, 3030, 3009, 2952, 2899, 1743, 1602, 1494,

1453, 1435, 1371, 1264, 1192, 1177, 1120, 1051, 1028, 1010, 955, 915; ^1H NMR (CDCl_3) δ 1.89-1.92 (1,m), 2.10-2.28 (1,m), 3.720 (3,s), 3.79-3.89 (1,m), 4.02-4.12 (1,m), 4.20-4.27 (1,m), 4.57-4.70 (2,m), 5.28 (1,s), 5.35 (1,s), 7.25-7.45 (10,m); ^{13}C NMR (CDCl_3) δ 30.19 (CH_2), 52.22 (CH_3), 67.12 (CH_2), 71.53 (CH_2), 75.47 (CH), 82.97 (CH), 104.38 (CH), 127.14 (CH), 127.67 (CH), 127.72 (CH), 128.38 (CH), 128.47 (CH), 136.58 (C), 137.88 (C), 171.34 (C).

For the more polar diastereomer 68b (R_f 0.23): $[\alpha]_D^{29} +102^\circ$ (c 4.26, CHCl_3); IR (CHCl_3) cm^{-1} 3064, 3028, 3011, 2952, 2900, 1747, 1600, 1494, 1453, 1435, 1371, 1348, 1269, 1170, 1114, 1049, 1028, 1015, 956, 910, 853; ^1H NMR (CDCl_3) δ 1.93-2.05 (1,m), 2.28-2.43 (1,m), 3.685 (3,s), 3.97-4.22 (3,m), 4.67 (2,s), 5.09 (1,s), 5.12 (1,s), 7.23-7.50 (10,m); ^{13}C NMR (CDCl_3) δ 30.21 (CH_2), 52.07 (CH_3), 67.32 (CH_2), 71.34 (CH_2), 76.69 (CH), 82.87 (CH), 104.50 (CH), 127.28 (CH), 127.53 (CH), 127.60 (CH), 128.29 (CH), 128.55 (CH), 128.63 (CH), 135.72 (C), 137.64 (C), 171.22 (C).

(R)-Pantolactone 3-Benzylloxyltetrahydrofuranyl Ethers (70a) and (70b).

This material was similarly prepared using (R)-pantolactone as the alcohol. PPTS (99.2 mg) was used as catalyst and the reaction required 5 days. Due to loss of solvent during the last overnight period the reaction underwent substantial

decomposition and the yield of the reaction suffered dramatically. After workup (as above) chromatography on 50 g of silica gel 60 eluted with 20% EtOAc/hexanes afforded the less polar diastereomer 70a (68.8 mg, 11.4%) and the more polar diastereomer 70b (34.7 mg, 5.7%) as yellow oils. Spectral data for 70a (R_f 0.52, 50% EtOAc/hexanes): $[\alpha]_D^{25} +55.1^\circ$ (c 3.44, CHCl_3); IR (CHCl_3) cm^{-1} 3027, 2986, 2963, 2899, 1787, 1494, 1478, 1463, 1453, 1437, 1399, 1371, 1343, 1268, 1123, 1065, 1027, 1013, 998, 960, 913, 813; ^1H NMR (CDCl_3) δ 1.022 (3,s), 1.144 (3,s), 1.93-2.06 (1,m), 2.13-2.28 (1,m), 3.85-4.01 (3,m), 4.09-4.19 (3,m), 4.50-4.72 (2,m), 5.58 (1,s), 7.25-7.40 (5,m); ^{13}C NMR (CDCl_3) δ 19.36 (CH_3), 22.73 (CH_3), 30.03 (CH_2), 39.83 (C), 66.97 (CH_2), 71.42 (CH_2), 76.13 (CH_2), 77.44 (CH), 82.35 (CH), 104.63 (CH), 127.58 (CH), 127.69 (CH), 128.29 (CH) 137.72 (C), 175.24 (C).

For 70b (R_f 0.49): $[\alpha]_D^{25} +19.2^\circ$ (c 1.74, CHCl_3); IR (CHCl_3) cm^{-1} 3026, 3013, 2962, 2900, 1784, 1494, 1462, 1453, 1371, 1267, 1123, 1070, 1027, 1012, 910; ^1H NMR (CDCl_3) δ 1.052 (3,s), 1.188 (3,s), 1.91-2.05 (1,m), 2.11-2.40 (1,m), 3.85-4.27 (6,m), 4.48-4.70 (2,m), 5.160 (1,s), 7.25-7.41 (5,m); ^{13}C NMR (CDCl_3) δ 19.53 (CH_3), 23.45 (CH_3), 29.91 (CH_2), 40.22 (C), 67.38 (CH_2), 71.63 (CH_2), 75.56 (CH_2), 77.41 (CH), 83.03 (CH), 105.82 (CH), 127.70 (CH), 127.82 (CH), 128.32 (CH), 128.46 (CH), 137.69 (C), 174.56 (C).

Methyl α -Hydroxybutanoate (2R,3S)-3-Benzoyloxytetrahydro-furanyl Ethers (71a) and (71b).

(2S,3R) Methyl 3-benzoyloxytetrahydrofuran-3-yl ether 66 (310.9 mg, 1.493 mmol), racemic methyl α -hydroxybutanoate (307.8 mg, 2.61 mmol), and TsOH (10.7 mg) were placed in 40 mL benzene in a flask equipped with a stir bar and a Dean-Stark trap. Molecular sieves (4Å) were placed in the Dean-Stark trap to bind to evolved methanol and the reaction was heated to reflux for 10 hours. The reaction mixture was then cooled to room temperature and chromatographed directly on 50 g of silica gel 60 eluted with 10% EtOAc/hexanes. Complete resolution of the product diastereomers from each other and from the other contaminants in the mixture then required chromatography 3 times on 50 g eluted with 10% EtOAc/hexanes and 4 times eluted with 20%. The less polar diastereomer 71a (158.7 mg, 36%) was collected as a yellow oil and the more polar diastereomer 71b (120.6 mg, 27%) as a colorless oil (63% combined yield). Spectral data for the 71a (R_f 0.39 in 20% EtOAc/hexanes; 0.17 in 10%): $[\alpha]_D^{25} +62.2^\circ$ (c 4.76, CHCl_3); IR (CHCl_3) cm^{-1} 3026, 3009, 2953, 2899, 1742, 1603, 1555, 1495, 1453, 1436, 1371, 1296, 1087, 1028, 956, 913, 855; ^1H NMR (CDCl_3) δ 0.93 (3,t, $J=7.3$ Hz), 1.60-1.87 (2,m), 1.89-2.04 (1,m), 2.10-2.29 (1,m), 3.74 (3,s), 3.87-3.97 (1,m), 4.02-4.24 (3,m), 4.55 (1,d, $J=11.9$ Hz), 4.62 (1,d, $J=11.9$ Hz), 5.20 (1,s), 7.20-7.38 (5,m); ^{13}C NMR (CDCl_3) δ 9.81 (CH_3), 26.02 (CH_2), 30.16 (CH_2),

51.76 (CH₃), 66.85 (CH₂), 71.41 (CH₂), 74.42 (CH), 82.81 (CH), 104.15 (CH), 127.61 (CH), 127.66 (CH), 128.32 (CH), 137.90 (C), 173.00 (C).

For the 71b (R_f 0.30 in 20%, 0.11 in 10%): $[\alpha]_D^{25} +5.53^\circ$ (c 3.87, CHCl₃); IR (CHCl₃) cm⁻¹ 3009, 2952, 1742, 1495, 1453, 1436, 1357, 1294, 1272, 1179, 1116, 1052, 1029, 920, 846; ¹H NMR (CDCl₃) δ 0.94 (3,t,J=7.4 Hz), 1.63-1.79 (2,m), 1.82-2.01 (1,m), 2.21-2.37 (1,m), 3.71 (3,s), 3.82-4.15 (4,m), 4.54 (2,s), 5.09 (1,s), 7.22-7.35 ((5,m); ¹³C NMR (CDCl₃) δ 9.54 (CH₃), 25.74 (CH₂), 30.25 (CH₂), 51.59 (CH₃), 67.14 (CH₂), 71.41 (CH₂), 77.31 (CH), 82.98 (CH), 106.61 (CH), 127.57 (CH), 127.63 (CH), 128.31 (CH), 137.72 (C), 173.39 (C).

Methyl Thiolactyl (2R,3S)-3-Benzylloxymethyl Tetrahydrofuranylethers (73a) and (73b).

This reaction was run as for the butanoate above but with 303.6 mg (1.458 mmol) of the methyl furanoside, 278.8 mg (3.162 mmol) racemic methyl thiolactate, and 14.3 mg TsOH. The reaction time was 5.5 hours. After workup the concentrate was chromatographed 3 times on 50 g silica gel 60 eluted with 20% EtOAc/hexanes to afford the inseparable trans products 73a and 73b (204.6 mg, 53%) as a yellow oil. A small amount (ca 10 mg) of the cis products was also isolated. Spectral data for the mixed 73a and 73b: ¹H NMR (CDCl₃) δ 1.46 and 1.51 (3,d,J=7.4 Hz, 7.0 Hz), 1.90-2.08 (1,m), 2.17-2.32 (1,m),

3.60-3.70 (1,m), 3.72 and 3.74 (3,s), 3.94-4.16 (3,m), 4.45-4.60 (2,m), 5.48 and 5.55 (1,s), 7.23-7.38 (5,m); ^{13}C NMR (CDCl_3) δ 17.26 and 17.90 (CH_3), 31.85 (CH_2), 39.48 and 41.21 (CH), 52.24 and 52.32 (CH_3), 66.46 (CH_2), 71.50 (CH_2), 83.65 and 83.96 (CH), 87.41 (CH), 127.64 (CH), 127.70 (CH), 128.34 (CH), 137.46 (C), 173.61 and 173.69 (C).

For the cis products: ^1H NMR (CDCl_3) δ 1.50 and 1.54 (3,d, $J=7.3$ Hz, 7.1 Hz), 2.00-2.22 (2,m), 3.58-3.70 (1,m), 3.72 and 3.75 (3,s), 3.80-3.94 (1,m), 4.03-4.18 (1,m), 4.20-4.32 (1,m), 4.50 and 4.52 (1,d, $J=11.7$ Hz, 11.7 Hz), 4.63 (1,d, $J=11.7$ Hz), 5.60-5.68 (1,d, $J=5.3$ Hz, 5.3 Hz), 7.22-7.40 (5,m).

Methyl α -Hydroxydodecanoate (2R,3S)-3-Benzylloxetetrahydrofuranyl Ethers (72a) and (72b).

(2S,3R) Methyl 3-benzylloxetetrahydrofuranyl ether 66 (309.9 mg, 1.488 mmol), racemic methyl α -hydroxydodecanoate (359.4 mg, 1.56 mmol), and TsOH (11.4 mg) were placed in 35 mL benzene in a flask equipped with a stir bar and a Dean-Stark trap. The reaction was heated to reflux for 2.5 hours with periodic removal of the benzene/methanol azeotrope. The reaction was then concentrated to 10 mL by distillation and was chromatographed on 50 g silica gel 60 eluted with 20% EtOAc/hexanes. Fractions containing the products were rechromatographed 4 times on 150 g of flash silica (twice eluted with 20% EtOAc/hexanes and twice with 10%) and 3 times

on 50 g of silica gel 60 (eluted with 10%). The difficulty with the separation was due to changing α values between the products and the starting materials; the α between the products was 1.51 (10% EtOAc/hexanes). The less polar diastereomer 72a (168.7 mg, 28%) was collected as a pale yellow oil, the more polar diastereomer 72b (135.1 mg, 22%) was a colorless oil. The combined yield for the reaction was 50%. Spectral data for 72a (R_f 0.30, 10% EtOAc/hexanes; 0.50 in 20%): $[\alpha]_D^{25} +47.7^\circ$ (c 4.49, CHCl_3); IR (CHCl_3) cm^{-1} 3026, 3009, 2925, 2854, 1739, 1495, 1453, 1436, 1372, 1229, 1200, 1107, 1028, 914; ^1H NMR (CDCl_3) δ 0.88 (3,t, $J=6.6$ Hz), 1.20-1.41 (16,m), 1.60-1.81 (2,m), 1.91-2.05 (1,m), 2.15 (2.29 (1,m), 3.74 (3,s), 3.86-3.96 (1,m), 4.06-4.17 (2,m), 4.25 (1,dd, $J=4.6$ Hz, 8.4 Hz), 4.55 (1,d, $J=11.9$ Hz), 4.62 (1,d, $J=11.9$ Hz), 5.18 (1,s), 7.23-7.40 (5,m); ^{13}C NMR (CDCl_3) δ 14.07 (CH_3), 22.65 (CH_2), 25.33 (CH_2), 29.04 (CH_2), 29.28 (CH_2), 29.42 (CH_2), 29.53 (CH_2), 30.22 (CH_2), 31.86 (CH_2), 32.68 (CH_2), 51.80 (CH_3), 66.92 (CH_2), 71.45 (CH_2), 73.24 (CH), 82.85 (CH), 104.13 (CH), 127.62 (CH), 127.70 (CH), 128.35 (CH), 137.93 (C), 173.27 (C).

For 72b (R_f 0.20 in 10%, 0.40 in 20%): $[\alpha]_D^{25} +16.8^\circ$ (c 3.10, CHCl_3); IR (CHCl_3) cm^{-1} 3028, 2925, 2854, 1742, 1495, 1453, 1436, 1355, 1280, 1230, 1176, 1105, 1028, 914, 849; ^1H NMR (CDCl_3) δ 0.878 (3,t, $J=6.5$ Hz), 1.15-1.50 (16,m), 1.61-1.77 (2,m), 1.89-2.05 (1,m), 2.22-2.38 (1,m), 3.71 (3,s), 3.85-4.08

(3,m), 4.10 (1,dd,J=2.4 Hz, 6.0 Hz), 4.54 (2,s), 5.09 (1,s), 7.22-7.41 (5,m); ^{13}C NMR (CDCl_3) δ 14.04 (CH_3), 22.62 (CH_2), 25.16 (CH_2), 29.20 (CH_2), 29.25 (CH_2), 29.36 (CH_2), 29.50 (CH_2), 30.34 (CH_2), 31.84 (CH_2), 32.59 (CH_2), 51.66 (CH_3), 67.21 (CH_2), 71.50 (CH_2), 76.27 (CH), 83.06 (CH), 106.76 (CH), 127.62 (CH), 127.69 (CH), 128.37 (CH), 137.79 (C), 173.68 (C).

(-)-Methyl α -Hydroxydodecanoate.

72a (137.6 mg, 0.3384 mmol) was dissolved in 8 mL of dry methanol and TsOH (250 μL of 1M TsOH in dry methanol, 47 mg, 0.25 mmol) was added. The reaction was stirred at 38°C for 4 days, cooled to room temperature, diluted with ether (75 mL), and washed with NaHCO_3 (20 mL of 25% saturated). The layers were separated and the ether phase was dried (MgSO_4), filtered, and volatiles removed in vacuo. The concentrate was chromatographed 4 times on 50 g silica gel 60 eluted with 10% EtOAc/hexanes to afford the recovered methyl furanosides (61.4 mg, 87%, 12:1 trans:cis) as a colorless oil and the product (69.2 mg, 89%) as a low-melting (approximately 20°C) solid. Spectral data for the dodecanoate (R_f 0.31, 20% EtOAc/hexanes): $[\alpha]_D^{25}$ -7.06° (c 1.50, CHCl_3); ^1H NMR (CDCl_3) δ 0.88 (3,t,J=6 Hz), 1.20-1.53 (16,m), 1.56-1.86 (2,m), 2.76 (1,d,J=5.8 Hz), 3.79 (3,s), 4.16-4.24 (1,m).

(+)-Methyl α -Hydroxydodecanoate.

This material was prepared as for the (-) isomer above using 72b (114.3 mg, 0.2811 mmol). The methyl furanoside was recovered in 80% yield and the product in 90% yield (58.4 mg). The product had a ^1H NMR spectrum similar to the (-) isomer but with rotation $[\alpha]_D^{25} +7.77$ (≤ 1.60 , CHCl_3).

APPENDIX A: X-Ray Crystal Structure Determination for the
Less Polar Diastereomer of (S)-Methyl Lactyl Tetrahydropyranyl
Ether

DATA COLLECTION

A white plate crystal of $C_{14}H_{18}O_4$ having approximate dimensions of 0.50 x 0.50 x 0.30 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) on a Syntex P2₁ diffractometer.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $20 < 2\theta < 30^\circ$. The orthorhombic cell parameters and calculated volume are: $a = 7.850(1)$, $b = 8.211(1)$, $c = 21.123(3) \text{ \AA}$, $V = 1361.4 \text{ \AA}^3$. For $Z = 4$ and F.W. = 250.30 the calculated density is 1.22 g/cm^3 . As a check on crystal quality, omega scans of several intense reflections were measured; the width at half-height was 0.19° , indicating good crystal quality. From the systematic absences of: $h00$, $h=2n+1$; $0k0$, $k=2n+1$; $00l$, $l=2n+1$; and from subsequent least-squares refinement, the space group was determined to be $P 2_12_12_1$ (No. 19).

The data were collected at a temperature of $23 \pm 1^\circ$ using the θ - 2θ scan technique. The scan rate varied from 2 to 8°/min. The variable scan rate allowed rapid data collection for intense reflections (where a fast scan rate was used) and assured good counting statistics for weak reflections (where a slow scan rate was used). Data were collected to a maximum 2θ of 50.0° . The scan range (in deg.) was determined as a function of 2θ to correct for the separation of the $K\alpha$ doublet. The scan width was calculated as follows:

$$\text{scan width} = \text{RNG1} + \text{RNG2} + (2\theta K\alpha_2 - 2\theta K\alpha_1) * \text{DISP}$$

The values of the parameters were $\text{RNG1} = 1.0$, $\text{RNG2} = 1.0$, and $\text{DISP} = 1.0$. The diameter of the incident beam collimator was 0.75 mm. The reflection intensity and standard deviations are computed using Eqns 2 and 3⁶⁵. The ratio of peak counting time to background counting time was 0.2 to 1.

DATA REDUCTION

A total of 1442 reflections were collected, of which 1419 were unique and not systematically absent. As a check on crystal and electronic stability 2 representative reflections were measured after every 98 reflections. The slope of the least-squares line through a plot of intensity versus time was

-1840 \pm 150 counts/hour which corresponds to a total loss in intensity of 7.8%. A linear decay correction was applied. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 0.8 cm⁻¹ for Mo K α radiation. No absorption correction was made.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods. A total of 8 atoms were located from an E-map. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares where the function minimized was $\sum w(|F_o| - |F_c|)^2$. The standard deviation on F^2 , $\sigma(F^2)$, is defined by Eqn 9 (page 144). The weights for each reflection were calculated using the counter weighting scheme, Eqn 8 (page 144). The uncertainty factor, p , was set to the value 0.040. Scattering factors were taken from Cromer and Waber⁶⁶. Anomalous dispersion effects were included in F_c ⁶⁷; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer⁶⁸. Only the 973 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 163 variable parameters and converged (largest parameter shift was 0.00 times esd) with

unweighted and weighted agreement factors of:

$$R1 = \Sigma |Fo - Fc| / \Sigma Fo = 0.039$$

$$R2 = \text{SQRT} (\Sigma w (Fo - Fc)^2 / \Sigma w Fo^2) = 0.047$$

The standard deviation of an observation of unit weight was 0.44. The highest peak in the final difference Fourier had a height of $0.18 \text{ e}^{-1}/\text{\AA}^3$ with an estimated error based on ΔF of 0.03; the minimum negative peak had a height of $-0.14 \text{ e}^{-1}/\text{\AA}^3$ with an estimated error based on ΔF of 0.03⁶⁹. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$, and various classes of indices showed no unusual trends.

All calculations were performed on a VAX computer using SDP/VAX⁷⁰.

EQUATIONS

$$\text{Eqn. 1} \quad \text{Scan Width} = \text{PNG1} + \text{PNG2} + (2\theta_{K\alpha_2} - 2\theta_{K\alpha_1}) * \text{DISP}$$

$$\text{Eqn. 2} \quad I = \left[\frac{\text{total scan count} - \left[\frac{\Sigma \text{ background counts}}{(\text{background:scan ratio})} \right]}{\left[\right]} \right] * \text{scan rate}$$

$$\text{Eqn. 3} \quad \sigma(I) = \left[\frac{\text{total scan count} + \left[\frac{\Sigma \text{ background counts}}{(\text{background:scan ratio})^2} \right]}{\left[\right]} \right]^{1/2} * \text{scan rate}$$

$$\text{Eqn. 4} \quad R1 = \frac{\Sigma |F_o| - |F_c|}{\Sigma |F_o|}$$

$$\text{Eqn. 5} \quad R2 = \left[\frac{\Sigma w (|F_o| - |F_c|)^2}{\Sigma w F_o^2} \right]^{1/2}$$

$$\text{Eqn. 6} \quad \text{ERRWT} = \text{GOF} = \left[\frac{\Sigma w (|F_o| - |F_c|)^2}{N_o - N_v} \right]^{1/2}$$

$$\text{Eqn. 7} \quad \text{minimize} \quad \Sigma w (|F_o| - |F_c|)^2$$

$$\text{Eqn. 8} \quad w = 4(F_o^2) / \sigma^2(F_o^2)$$

$$\text{Eqn. 9} \quad \sigma(F^2) = (\sigma^2(I) + (pF^2)^2)^{1/2}$$

Table of Experimental Details

A. Crystal Data

C14 H18 O4

F.W. 250.30 $F(000) = 536$

crystal dimensions: 0.50 x 0.50 x 0.30 mm

peak width at half-height = 0.19° Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$)temperature = $23 \pm 1^\circ$

orthorhombic space group P 21 21 21

 $a = 7.850 (1) \text{ \AA}$ $b = 8.211 (1) \text{ \AA}$ $c = 21.123 (3) \text{ \AA}$ $V = 1361.4 \text{ \AA}^3$ $Z = 4$ $\rho_{\text{calc}} = 1.22 \text{ g/cm}^3$ $\mu = 0.8 \text{ cm}^{-1}$

B. Intensity Measurements

Instrument:	Syntex-Nicolet P2 ₁ diffractometer
Monochromator:	Graphite crystal, incident beam
Scan type:	θ - 2θ
Scan rate:	2 - 8°/min
Scan width, deg:	2.0 + (2 θ K α_2 -2 θ K α_1)
Maximum 2 θ :	50.0°
No. of refl. measured:	1442 total, 1419 unique
Corrections:	
	Lorentz-polarization
	Linear decay

C. Structure Solution and Refinement

Solution:	Direct methods
Refinement:	Full-matrix least-squares
Minimization function:	$\sum w(F_o - F_c)^2$
Least-squares weights:	$4F_o^2 / \sum^2(F_o^2)$
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	973 with $F_o^2 > 3.0\sigma(F_o^2)$
Parameters refined:	163
Unweighted agreement factor:	0.039
Weighted agreement factor:	0.047
Esd of obs. of unit weight:	0.44
Convergence, largest shift:	0.00σ
High peak in final diff. map:	$0.18 (3) \text{ e}^{-1}/\text{\AA}^3$
Low peak in final diff. map:	$-0.14 (0) \text{ e}^{-1}/\text{\AA}^3$
Computer hardware:	VAX
Computer software:	SDP/VAX (Enraf-Nonius)

Positional Parameters With Estimated Standard Deviations

Atom	x	y	z	B(Å ²)
O1	0.5670(3)	0.3476(3)	-0.0204(1)	4.41(5)
O2	0.5848(3)	0.4782(3)	0.0784(1)	3.74(4)
O3	0.6600(4)	0.0844(3)	0.1333(1)	5.21(6)
O4	0.4695(4)	0.2573(4)	0.1725(1)	6.40(7)
C1	0.6645(5)	0.4639(5)	-0.0561(2)	4.70(8)
C2	0.5524(5)	0.5977(5)	-0.0826(2)	5.21(9)
C3	0.4550(5)	0.6809(5)	-0.0293(2)	5.15(9)
C4	0.3597(5)	0.5544(5)	0.0095(2)	4.60(8)
C5	0.4750(5)	0.4169(4)	0.0299(2)	4.00(7)
C6	0.6945(4)	0.3575(4)	0.1041(1)	3.34(6)
C7	0.5927(5)	0.2308(4)	0.1406(2)	3.82(7)
C8	0.5798(7)	-0.0496(5)	0.1670(2)	7.1(1)
C9	0.8199(4)	0.4429(4)	0.1480(1)	3.15(6)
C10	0.7595(5)	0.5343(5)	0.1987(1)	4.39(8)
C11	0.8721(6)	0.6135(5)	0.2379(2)	5.35(9)
C12	1.0448(5)	0.6024(5)	0.2277(2)	5.06(9)
C13	1.1054(5)	0.5110(5)	0.1773(2)	4.64(8)
C14	0.9925(4)	0.4320(4)	0.1374(2)	3.80(7)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:
 $(4/3) * [a^2 * B(1,1) + b^2 * B(2,2) + c^2 * B(3,3) + ab(\cos \gamma) * B(1,2) + ac(\cos \beta) * B(1,3) + bc(\cos \alpha) * B(2,3)]$

Positional Parameters With Estimated Standard Deviations

Atom	x	y	z	B(Å ²)
H1	0.721	0.409	-0.090	5.0*
H2	0.747	0.512	-0.029	5.0*
H3	0.472	0.550	-0.111	5.0*
H4	0.620	0.675	-0.105	5.0*
H5	0.378	0.758	-0.046	5.0*
H6	0.534	0.735	-0.002	5.0*
H7	0.271	0.511	-0.016	5.0*
H8	0.311	0.604	0.046	5.0*
H9	0.407	0.331	0.046	5.0*
H10	0.753	0.302	0.071	5.0*
H11	0.639	-0.148	0.158	5.0*
H12	0.584	-0.027	0.211	5.0*
H13	0.465	-0.060	0.154	5.0*
H14	0.640	0.540	0.206	5.0*
H15	0.829	0.676	0.272	5.0*
H16	1.122	0.659	0.254	5.0*
H17	1.225	0.500	0.171	5.0*
H18	1.033	0.371	0.102	5.0*

*Atoms were refined isotropically.

Table of General Displacement Parameter Expressions - U's

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
O1	0.075(2)	0.046(1)	0.047(1)	-0.002(2)	-0.008(1)	-0.006(1)
O2	0.054(1)	0.044(1)	0.044(1)	0.004(1)	-0.009(1)	-0.004(1)
O3	0.081(2)	0.043(1)	0.074(1)	0.009(1)	0.020(1)	0.015(1)
O4	0.073(2)	0.070(2)	0.100(2)	0.005(2)	0.040(1)	0.013(2)
C1	0.066(2)	0.061(2)	0.052(2)	-0.002(2)	0.005(2)	-0.003(2)
C2	0.073(2)	0.066(2)	0.059(2)	-0.009(2)	-0.001(2)	0.013(2)
C3	0.068(2)	0.057(2)	0.070(2)	0.009(2)	-0.005(2)	0.009(2)
C4	0.049(2)	0.068(2)	0.057(2)	0.005(2)	-0.005(2)	0.005(2)
C5	0.056(2)	0.050(2)	0.047(2)	-0.011(2)	-0.009(2)	0.002(2)
C6	0.050(2)	0.039(2)	0.038(1)	0.002(2)	-0.001(2)	0.001(2)
C7	0.049(2)	0.051(2)	0.044(2)	0.005(2)	-0.002(2)	-0.001(2)
C8	0.109(4)	0.056(2)	0.105(3)	-0.004(3)	0.020(3)	0.027(2)
C9	0.052(2)	0.034(2)	0.033(1)	0.005(2)	-0.000(1)	0.002(1)
C10	0.061(2)	0.061(2)	0.045(2)	0.009(2)	-0.000(2)	-0.009(2)
C11	0.086(3)	0.065(2)	0.052(2)	0.011(3)	-0.005(2)	-0.015(2)
C12	0.076(2)	0.056(2)	0.060(2)	0.001(2)	-0.020(2)	-0.006(2)
C13	0.054(2)	0.061(2)	0.062(2)	0.003(2)	-0.013(2)	0.000(2)
C14	0.049(2)	0.049(2)	0.047(2)	0.005(2)	0.000(2)	-0.001(2)

The form of the anisotropic displacement parameter is:
 $\exp[-2\pi^2\{h^2a^2U(1,1)+k^2b^2U(2,2)+l^2c^2U(3,3)+2hkabU(1,2)+2hlacU(1,3)+2klbcU(2,3)\}]$ where a, b, and c are reciprocal lattice constants.

Table of Bond Distances in Angstroms

<u>Atom 1</u>	<u>Atom 2</u>	<u>Distance</u>	<u>Atom 1</u>	<u>Atom 2</u>	<u>Distance</u>
O1	C1	1.438(7)	C4	C5	1.511(8)
O1	C5	1.405(7)	C6	C7	1.522(8)
O2	C5	1.430(7)	C6	C9	1.523(8)
O2	C6	1.421(6)	C9	C10	1.392(7)
O3	C7	1.322(7)	C9	C14	1.376(8)
O3	C8	1.454(8)	C10	C11	1.375(9)
O4	C7	1.198(7)	C11	C12	1.38(1)
C1	C2	1.514(9)	C12	C13	1.386(9)
C2	C3	1.523(9)	C13	C14	1.384(8)
C3	C4	1.519(9)			

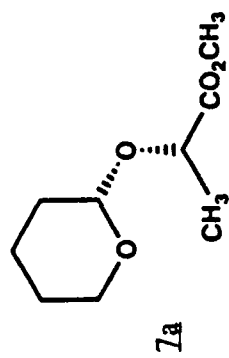
Numbers in parentheses are estimated standard deviations in the least significant digits. Carbon-hydrogen bond lengths were fixed at 0.950 angstroms.

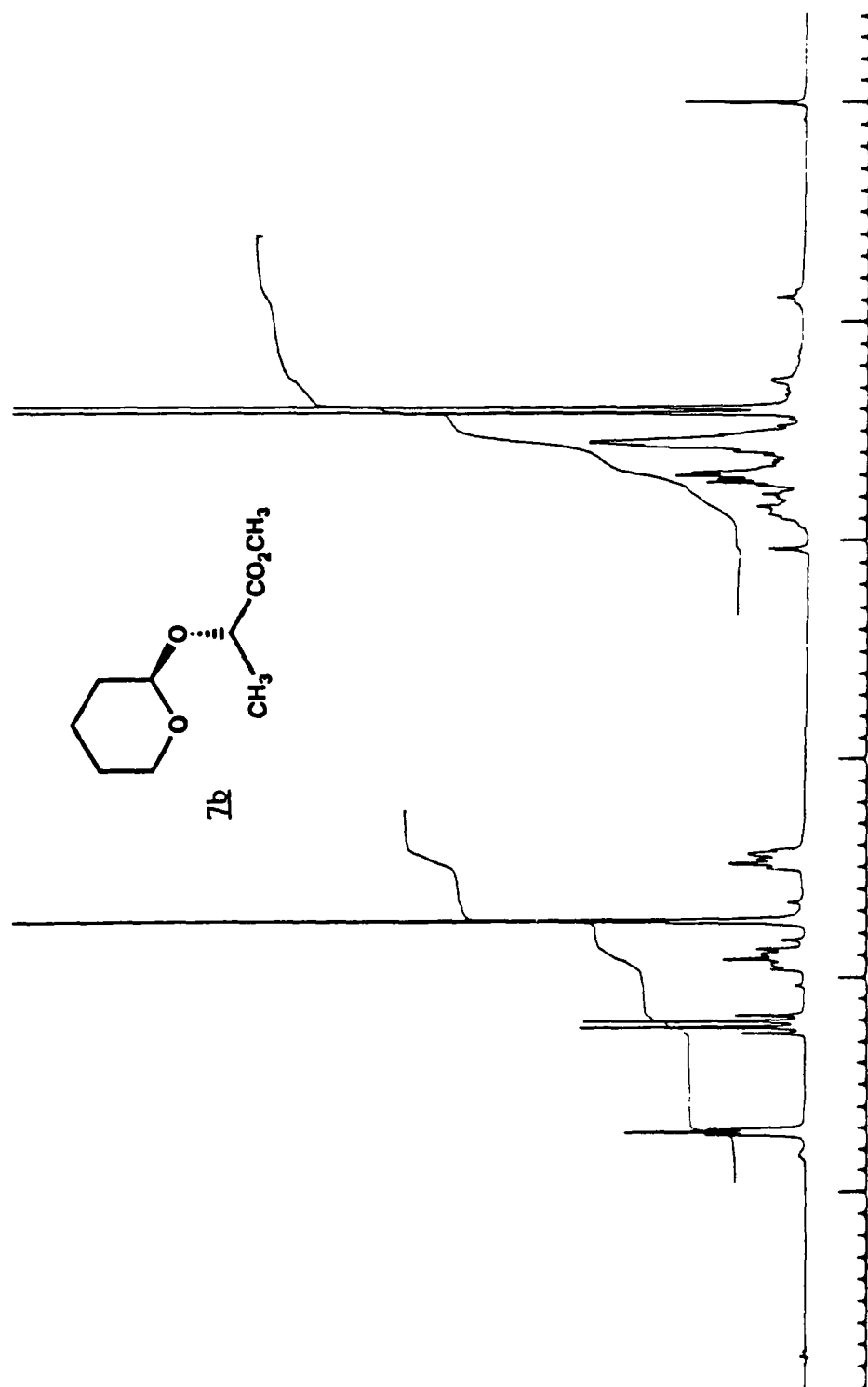
Table of Bond Angles in Degrees

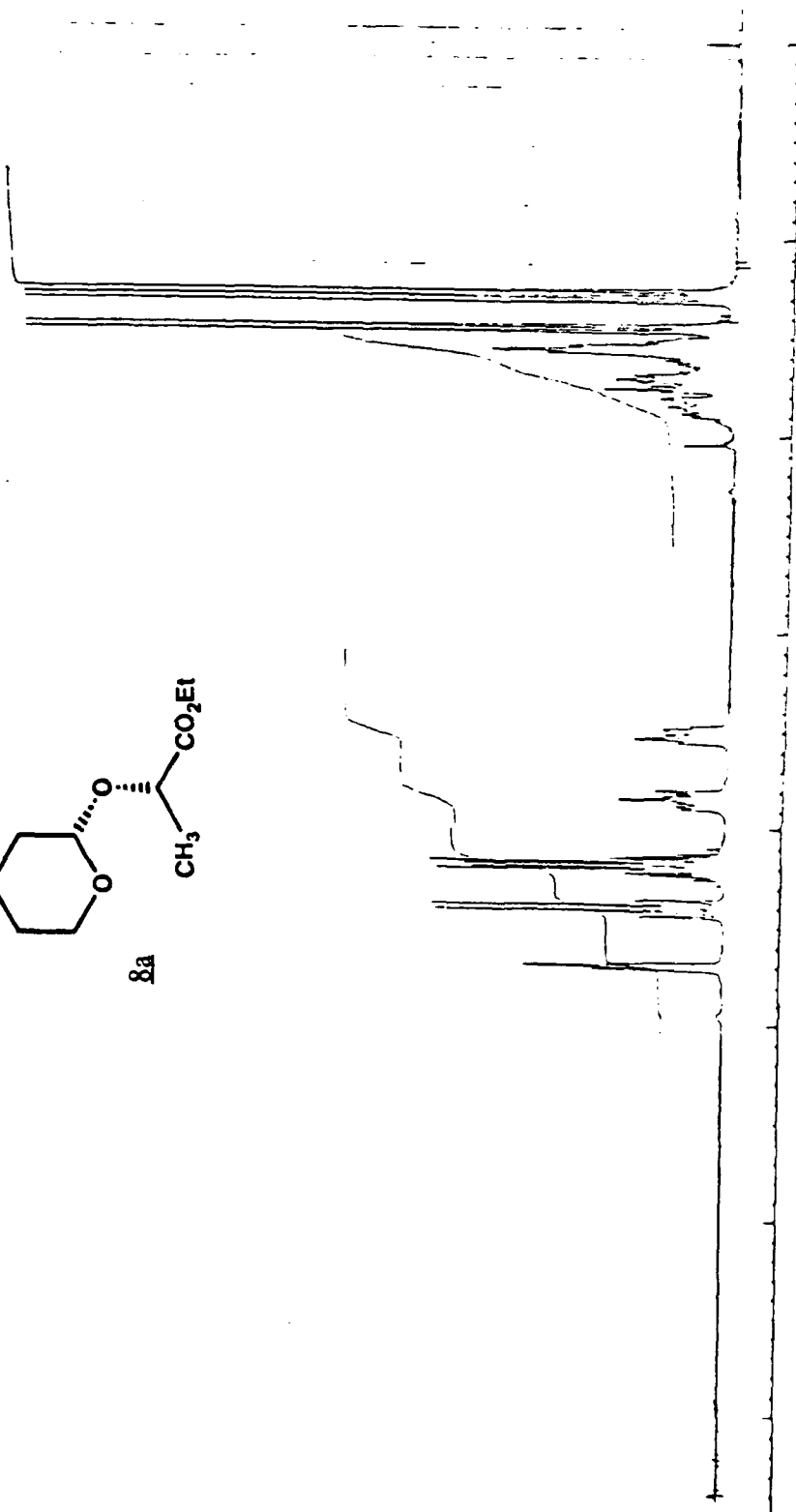
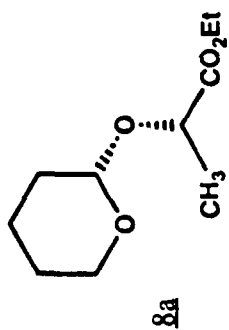
Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	O1	C5	113.7(4)	C7	C6	C9	110.3(4)
C5	O2	C6	113.2(4)	O3	C7	O4	123.7(6)
C7	O3	C8	117.2(5)	O3	C7	C6	110.6(5)
O1	C1	C2	111.5(5)	O4	C7	C6	125.7(6)
C1	C2	C3	110.2(5)	C6	C9	C10	119.8(6)
C2	C3	C4	109.8(5)	C6	C9	C14	120.5(5)
C3	C4	C5	111.7(5)	C10	C9	C14	119.7(6)
O1	C5	O2	111.9(5)	C9	C10	C11	120.0(7)
O1	C5	C4	113.2(5)	C10	C11	C12	120.4(6)
O2	C5	C4	107.6(5)	C11	C12	C13	119.7(7)
O2	C6	C7	110.6(5)	C12	C13	C14	120.1(6)
O2	C6	C9	107.6(4)	C9	C14	C13	120.0(6)

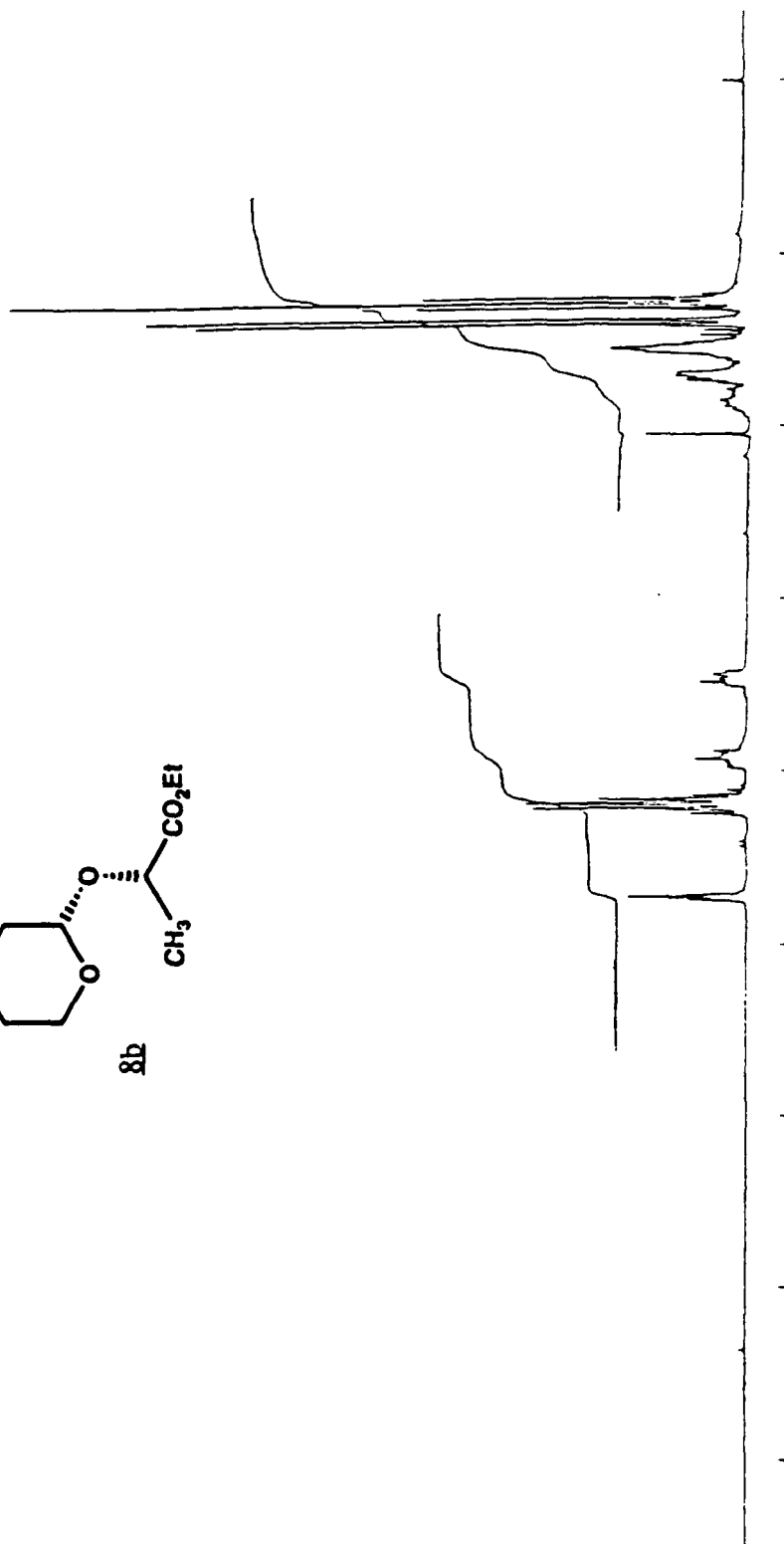
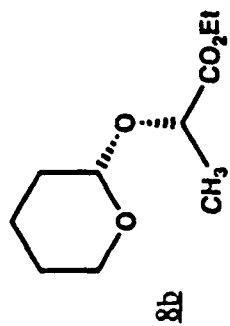
Numbers in parentheses are estimated standard deviations in the least significant digits. Hydrogen atoms were ridden on their respective carbon atoms.

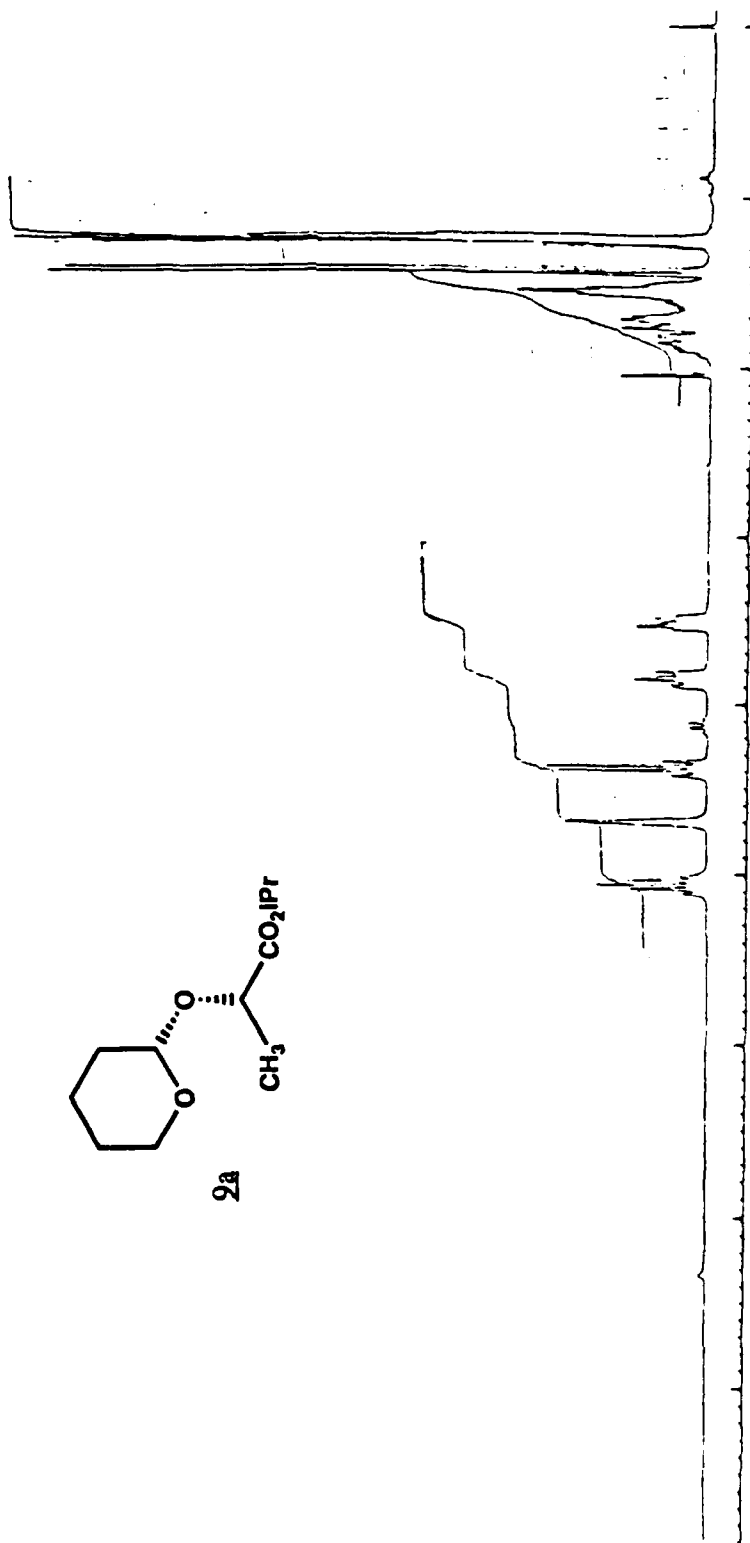
APPENDIX B: ^1H NMR OF SELECTED COMPOUNDS

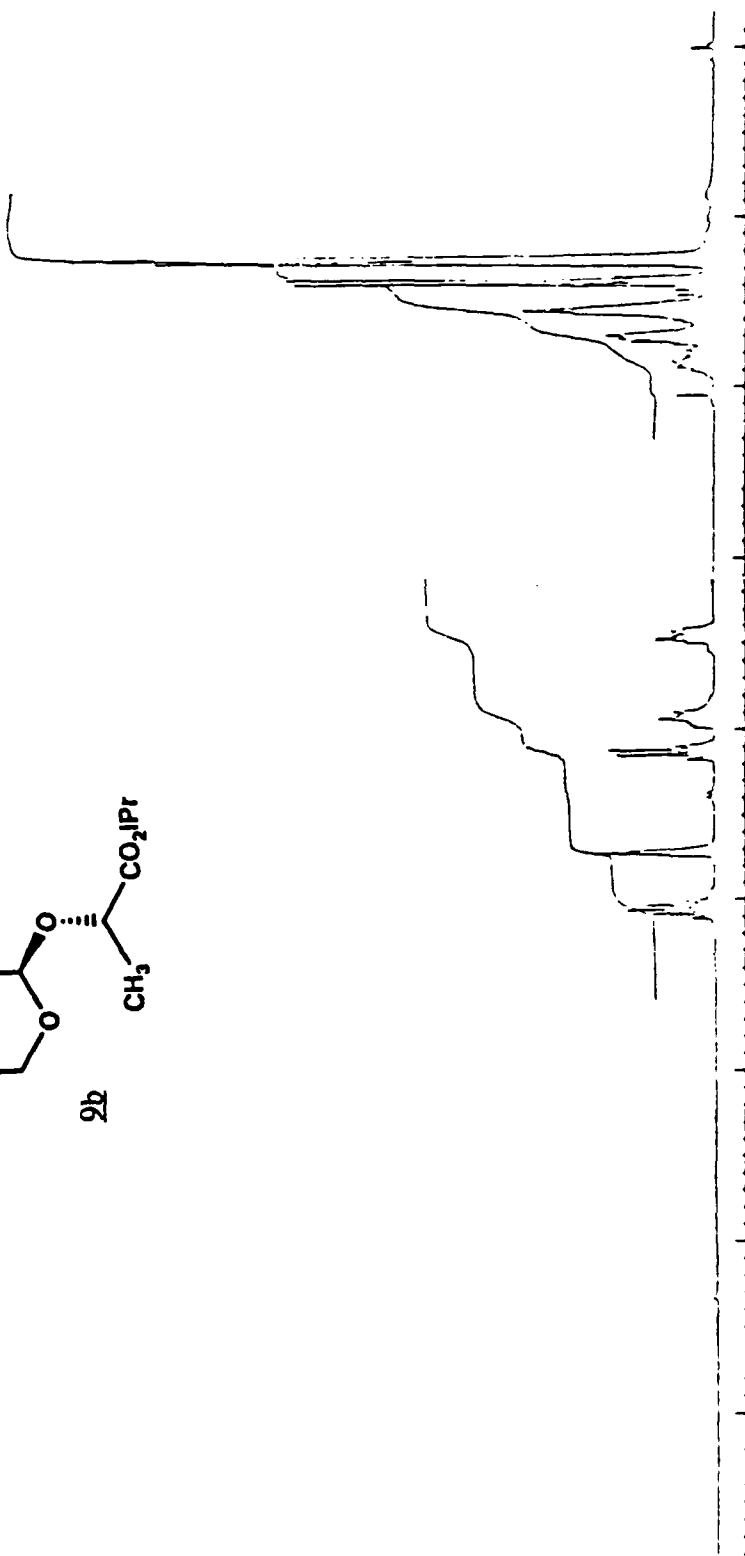
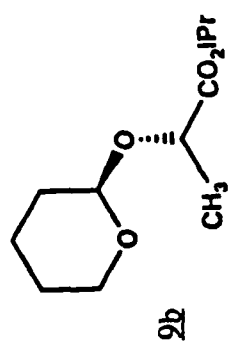


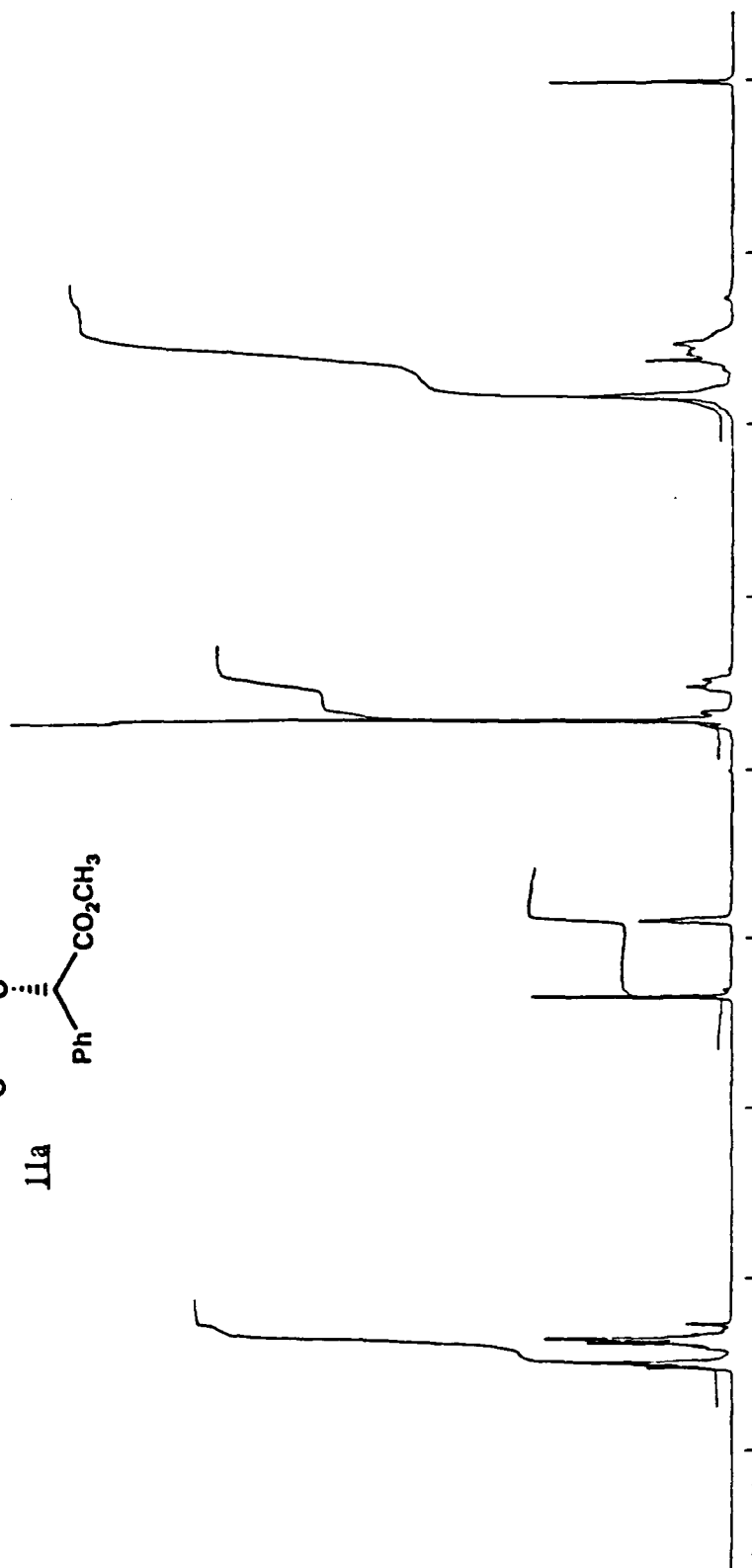
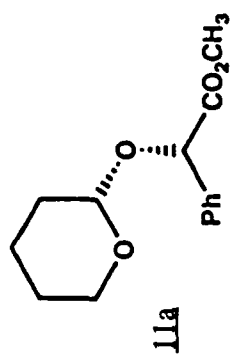


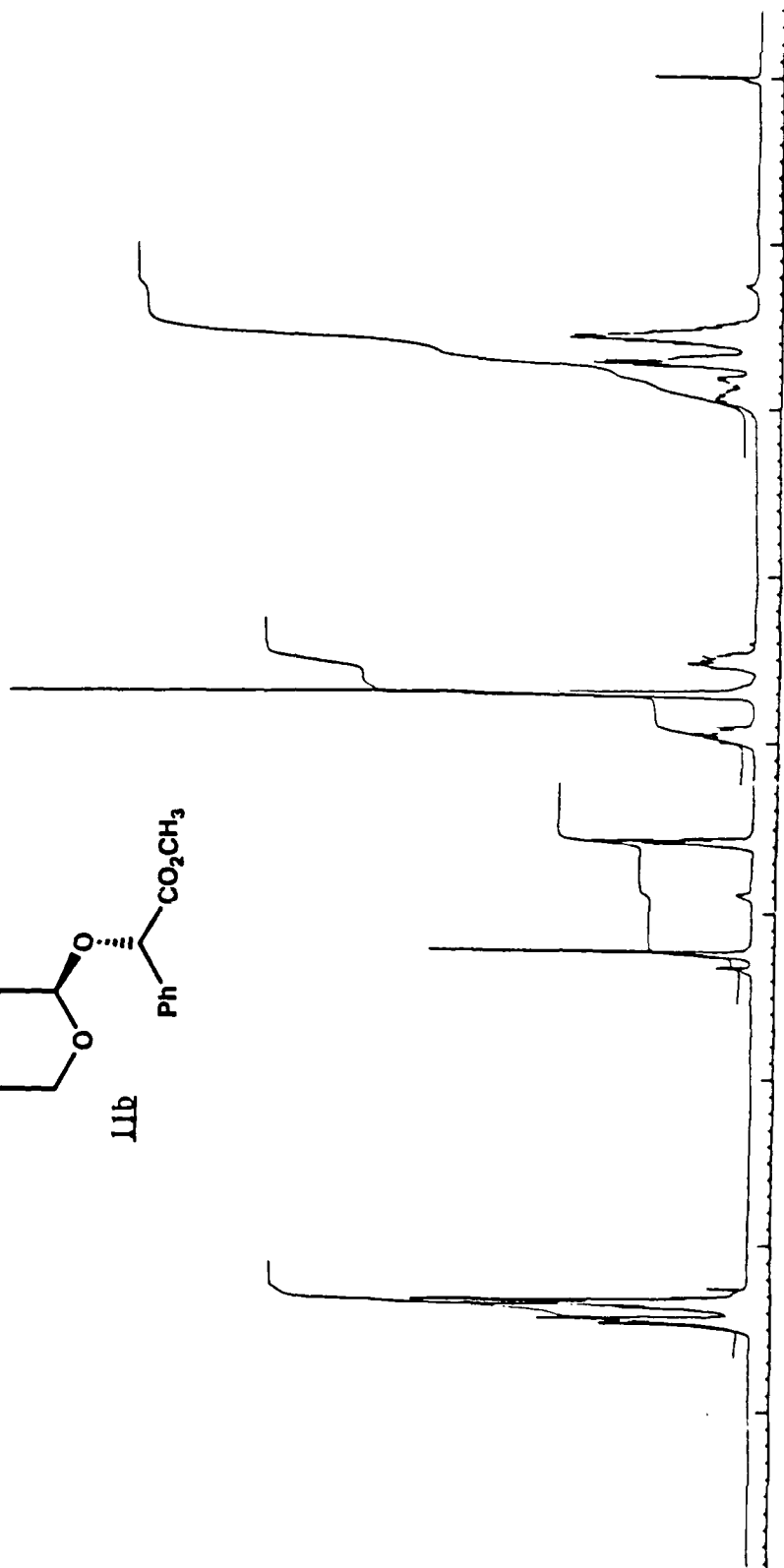
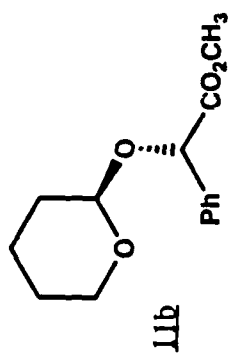


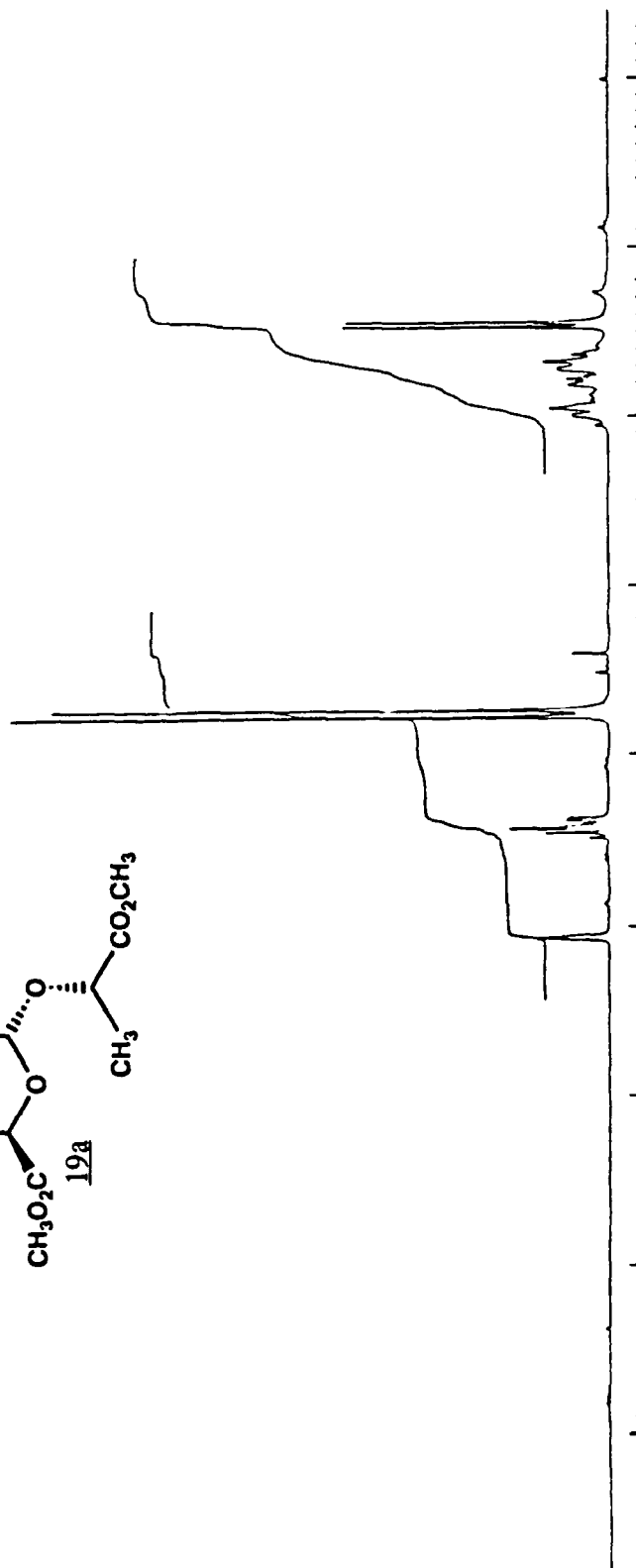
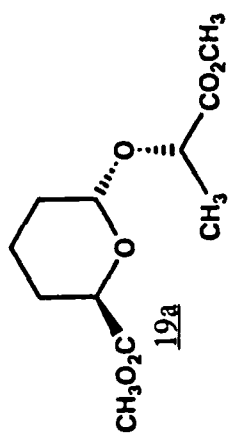


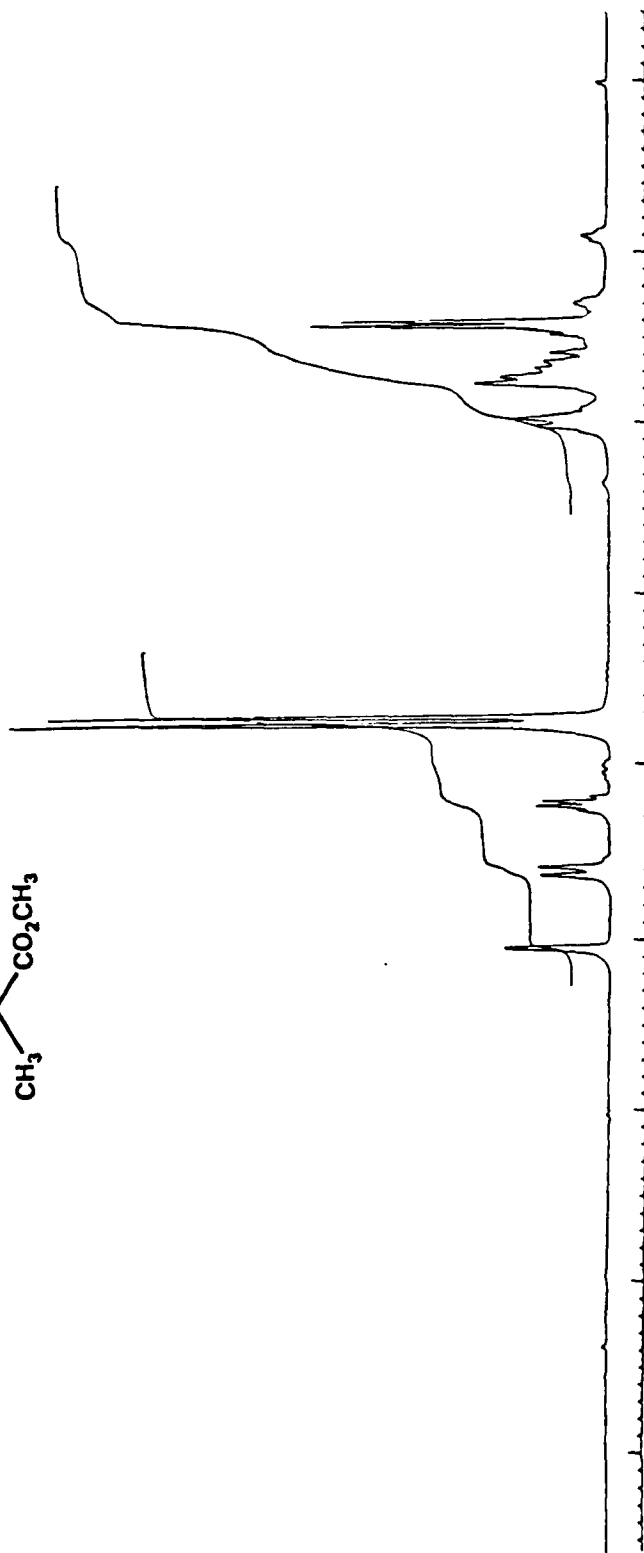
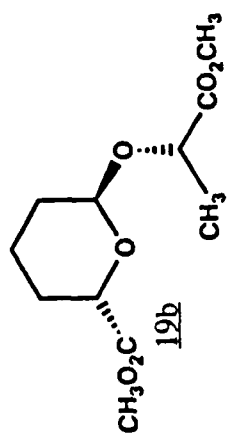


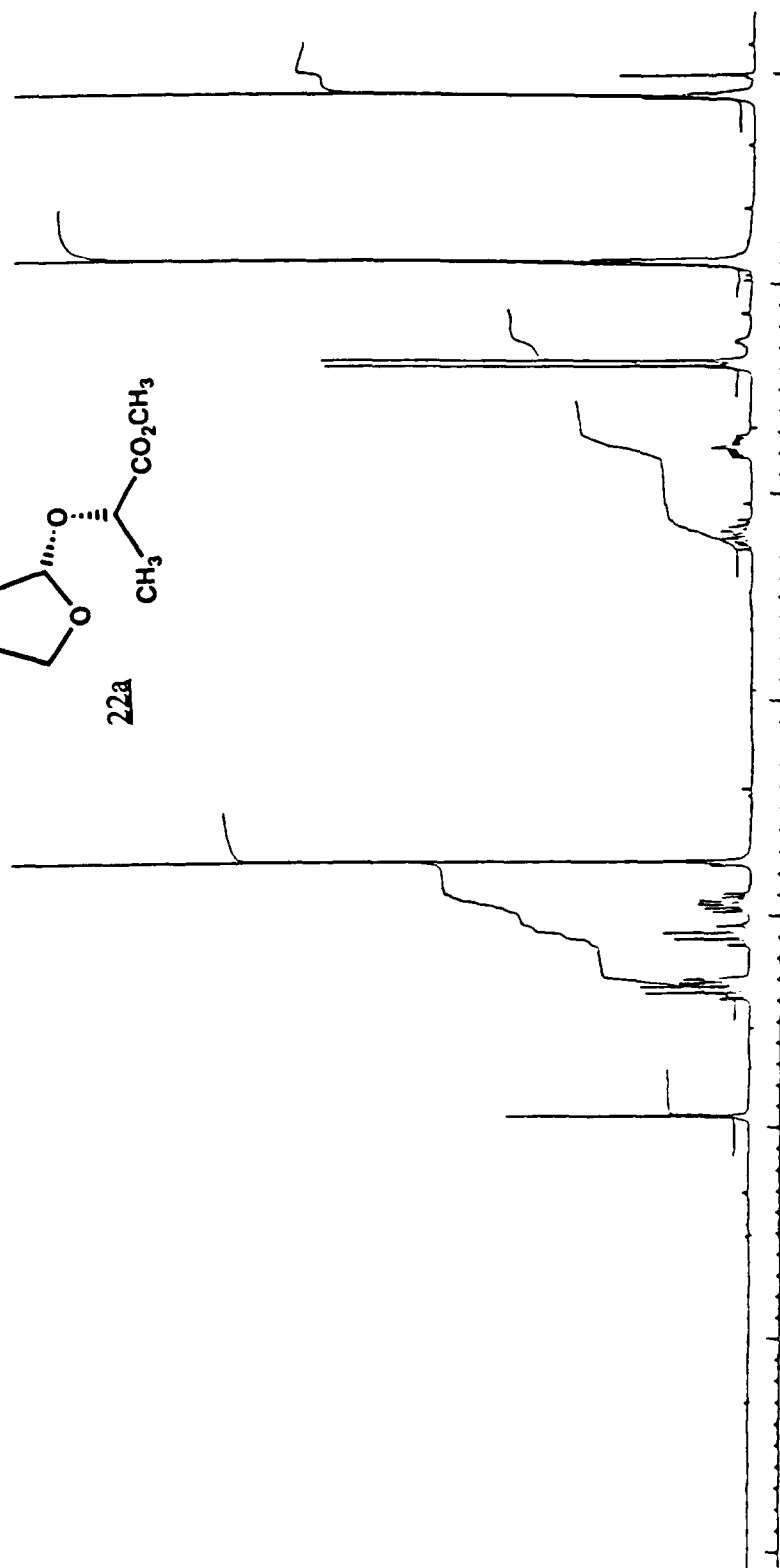
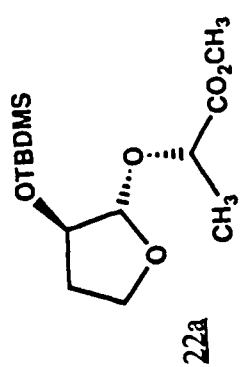


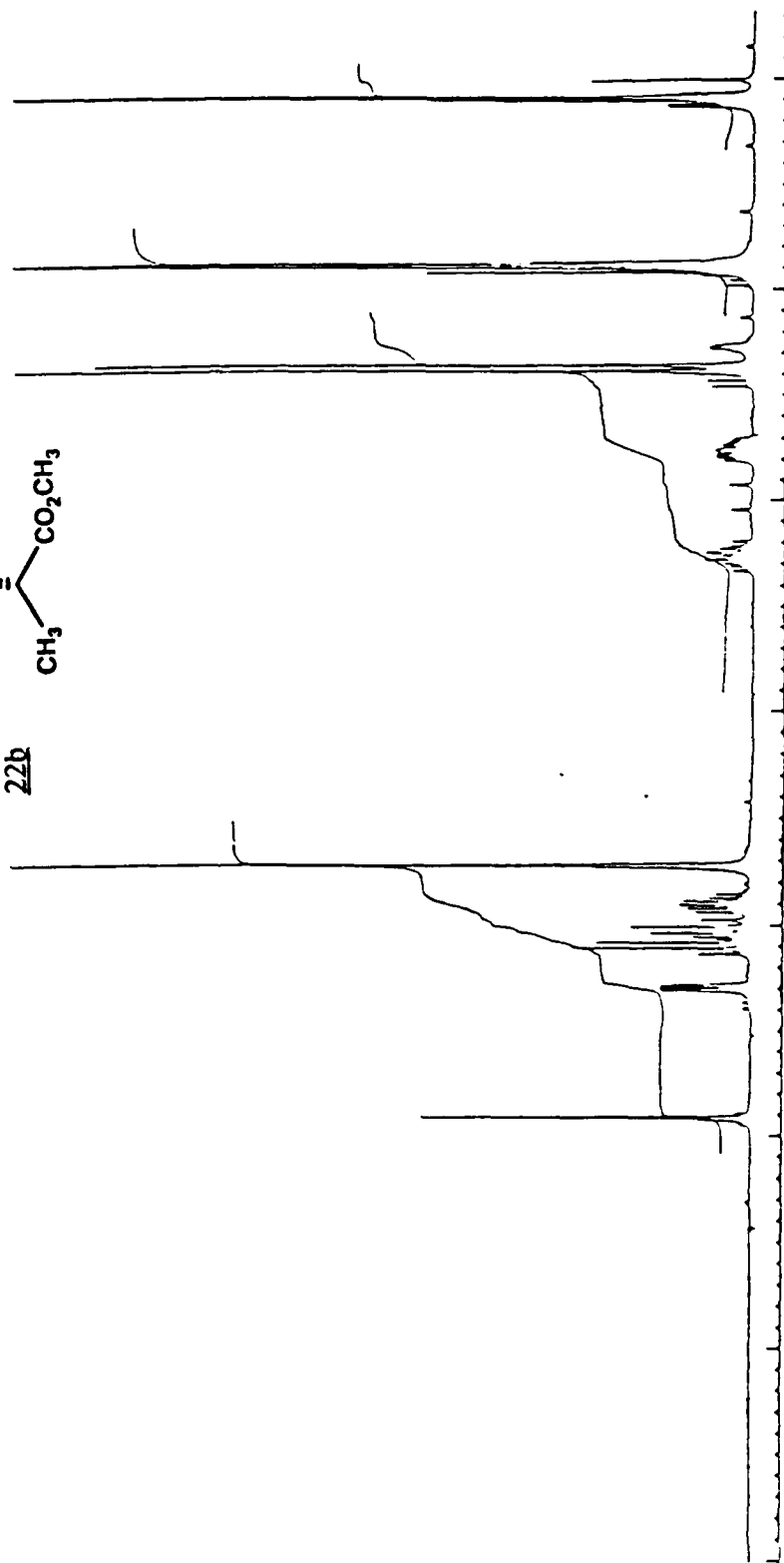
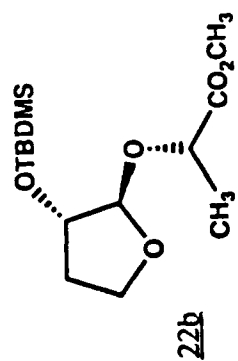


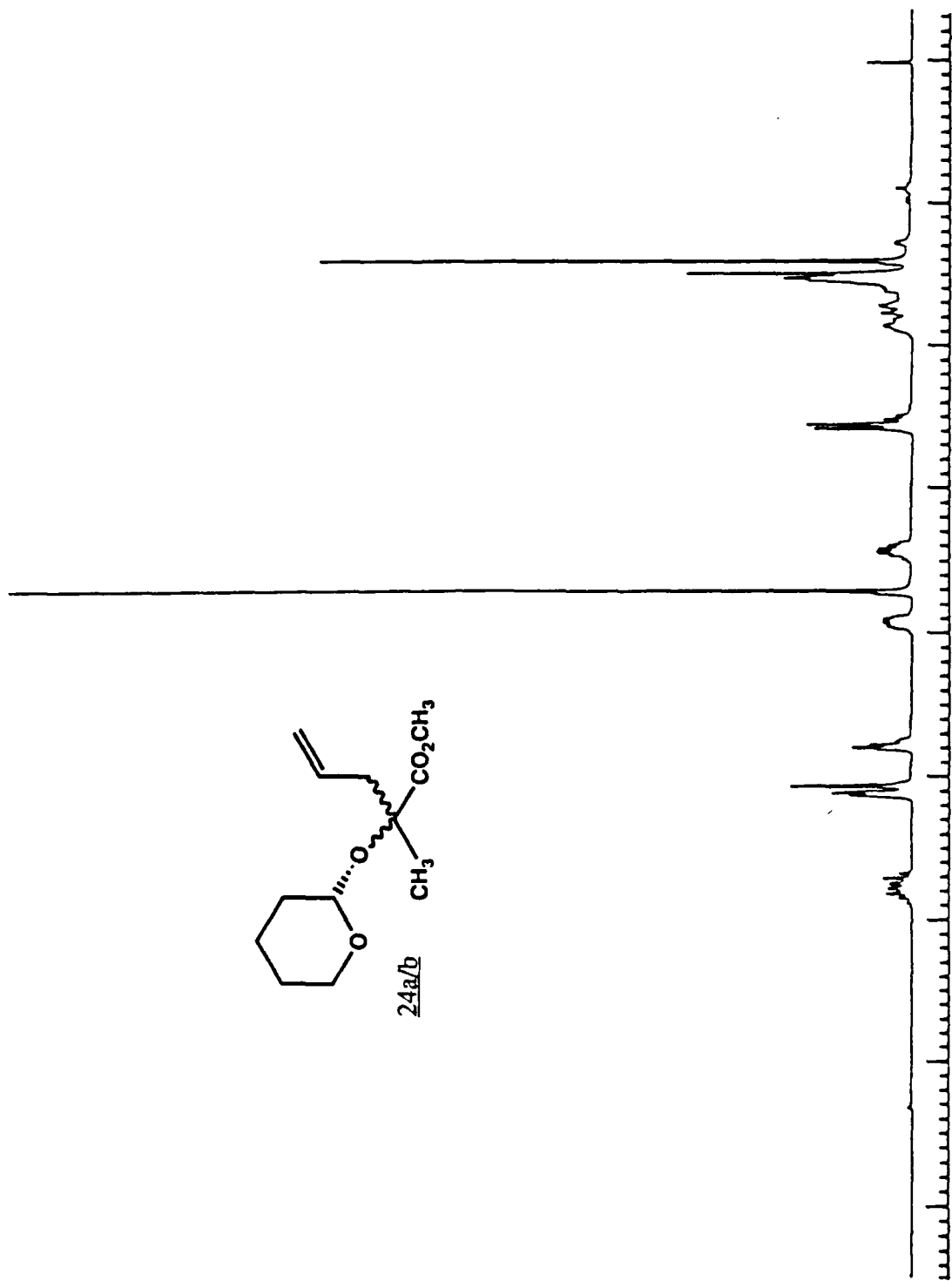
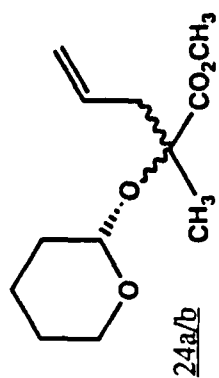


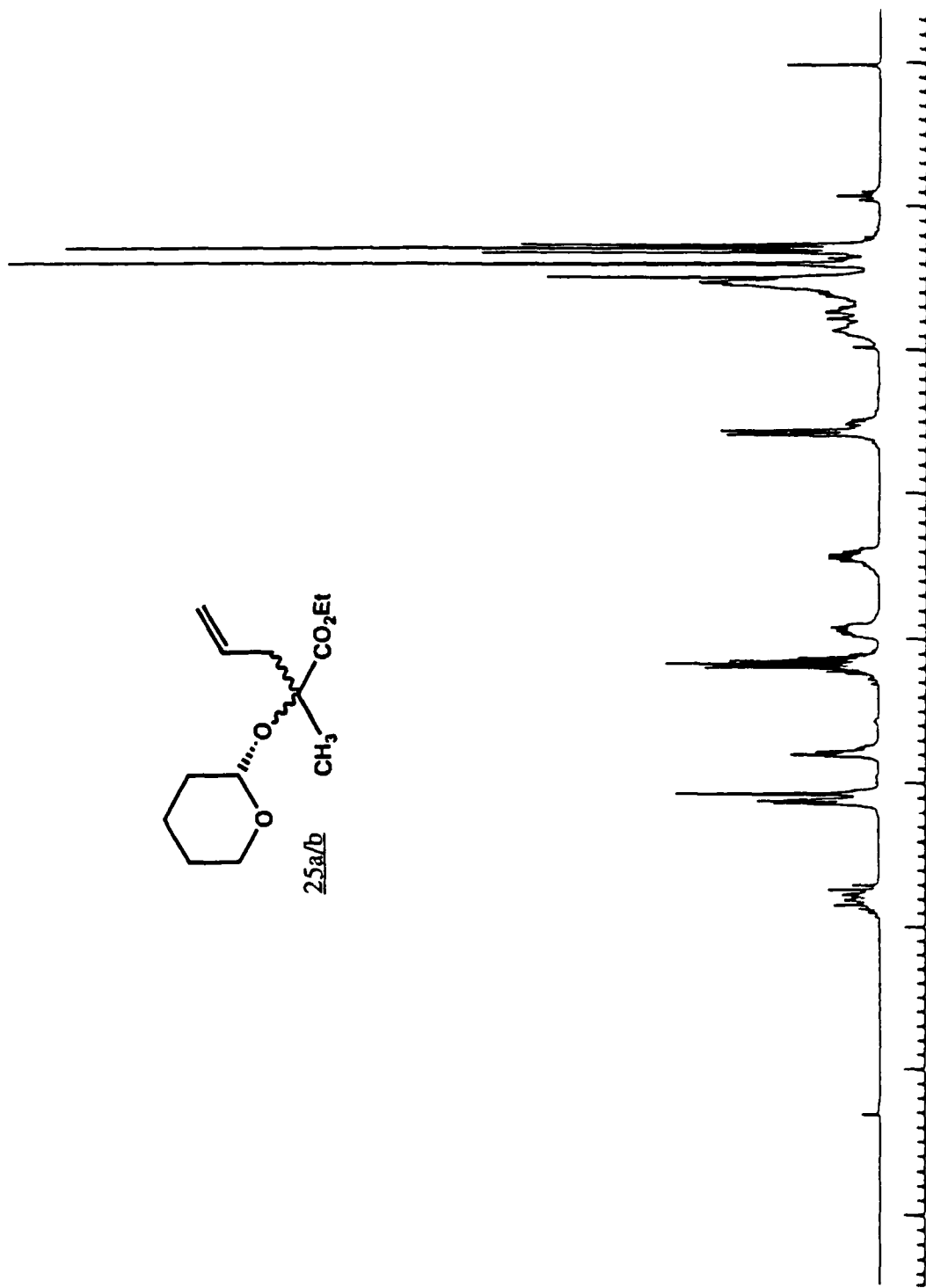
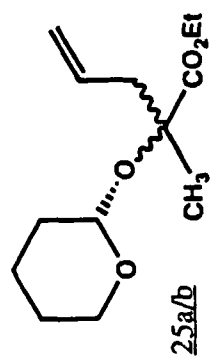


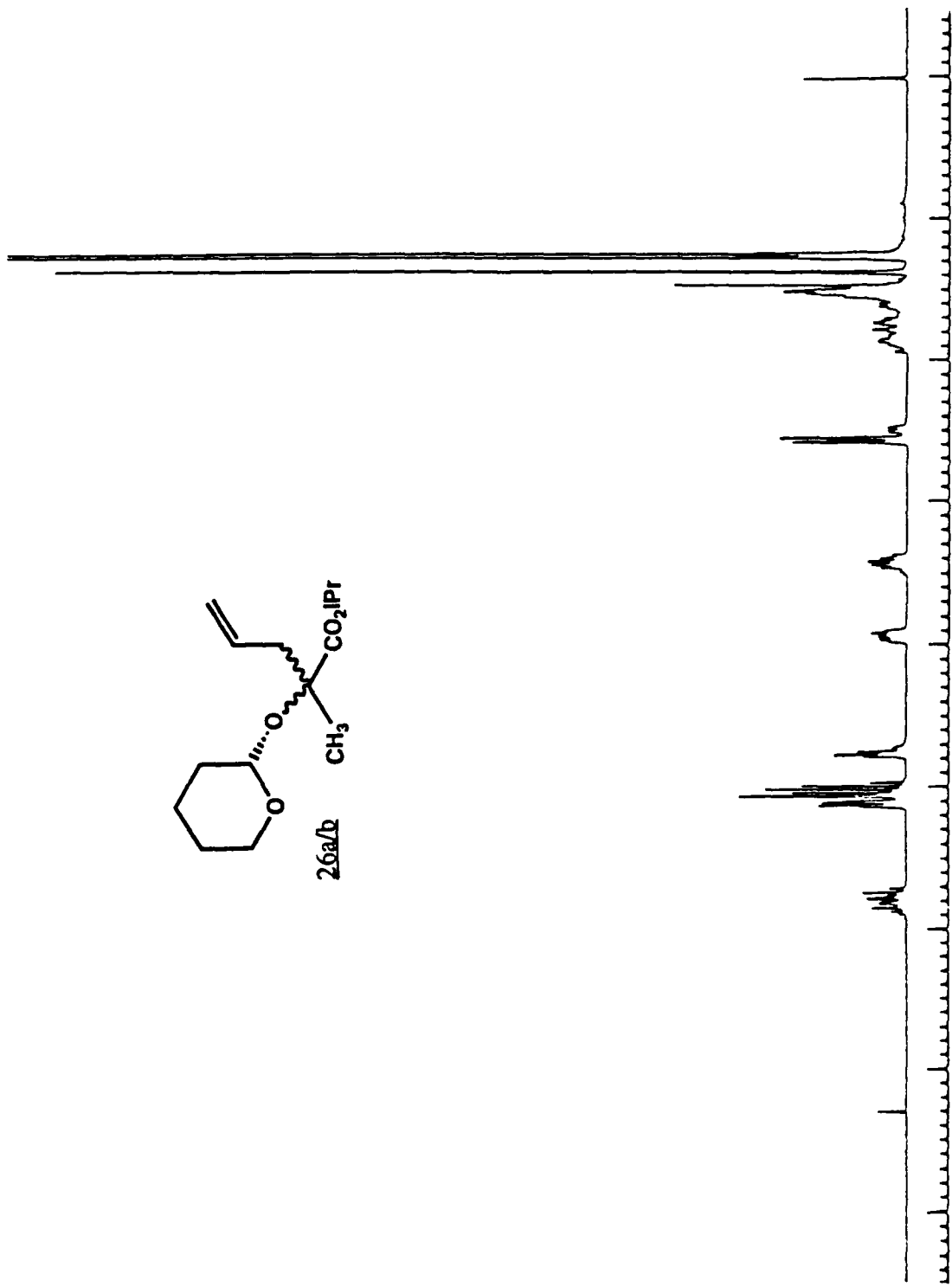
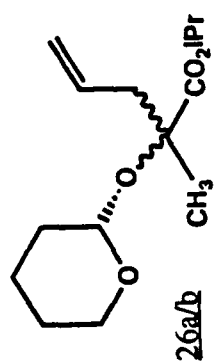


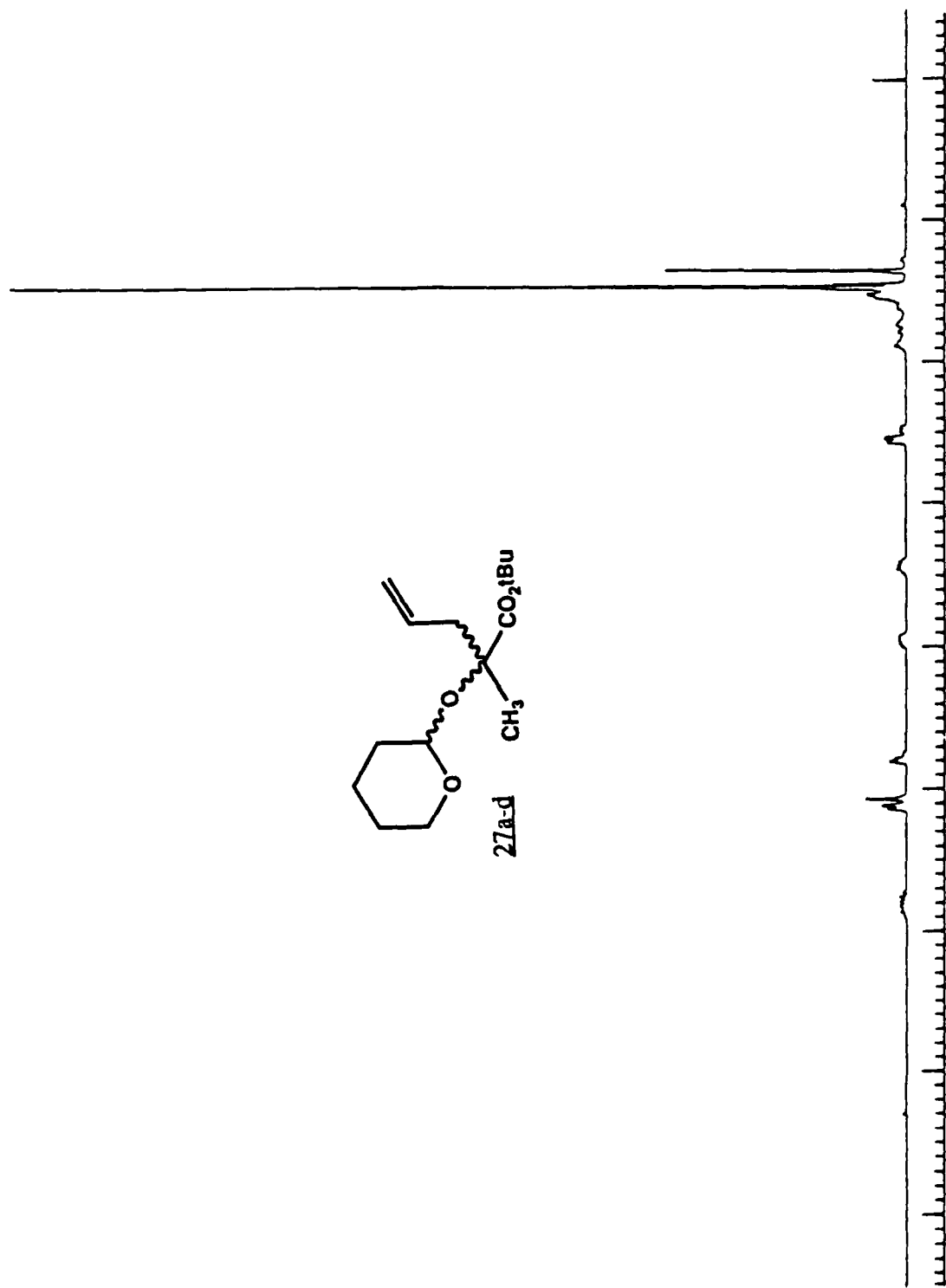
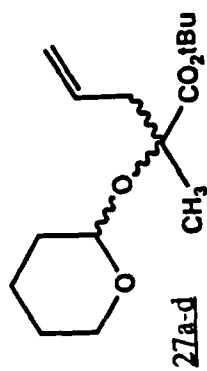


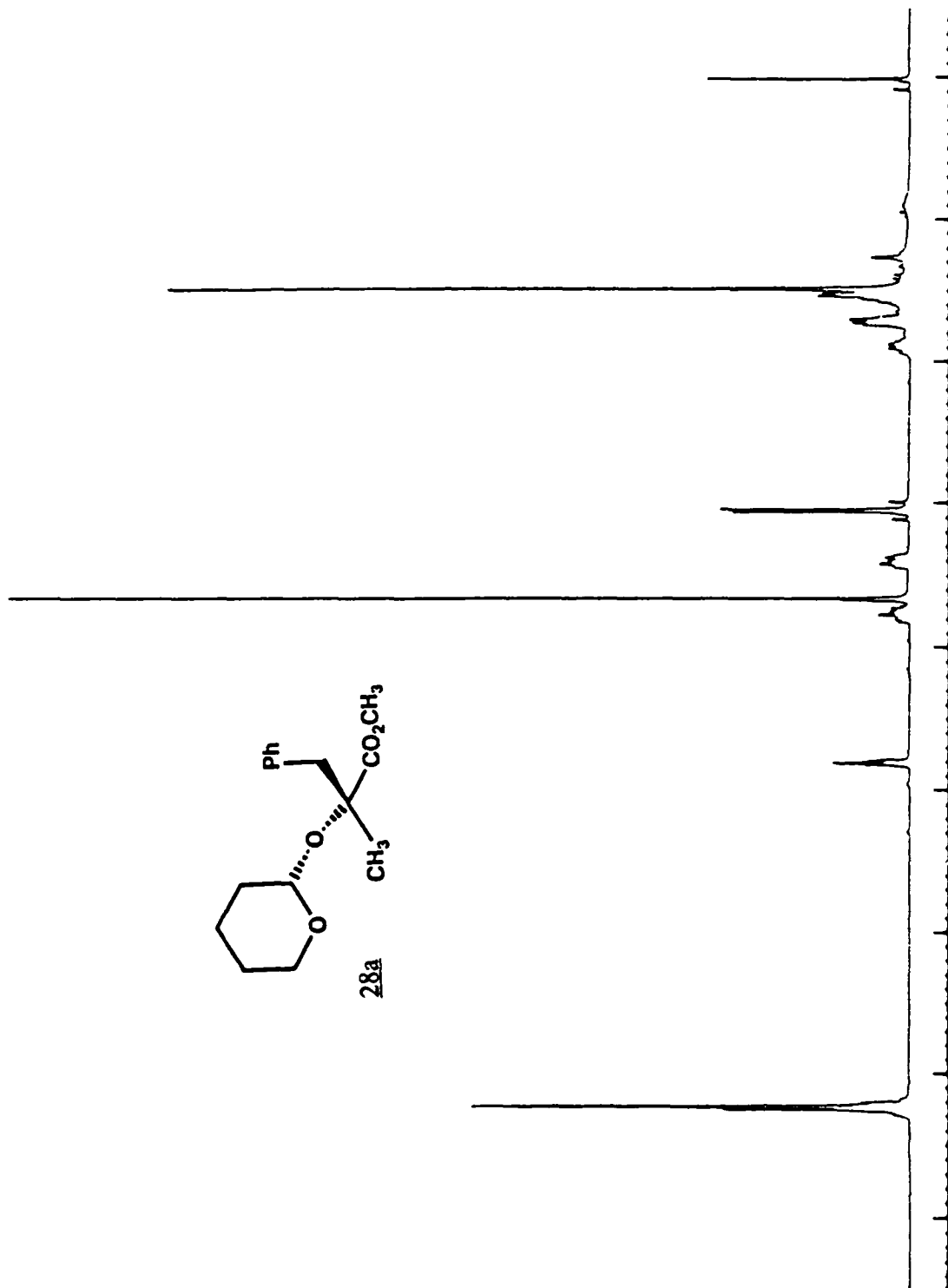
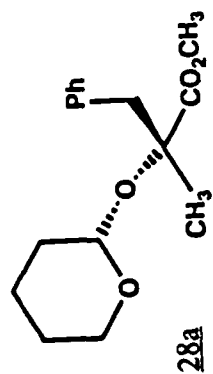


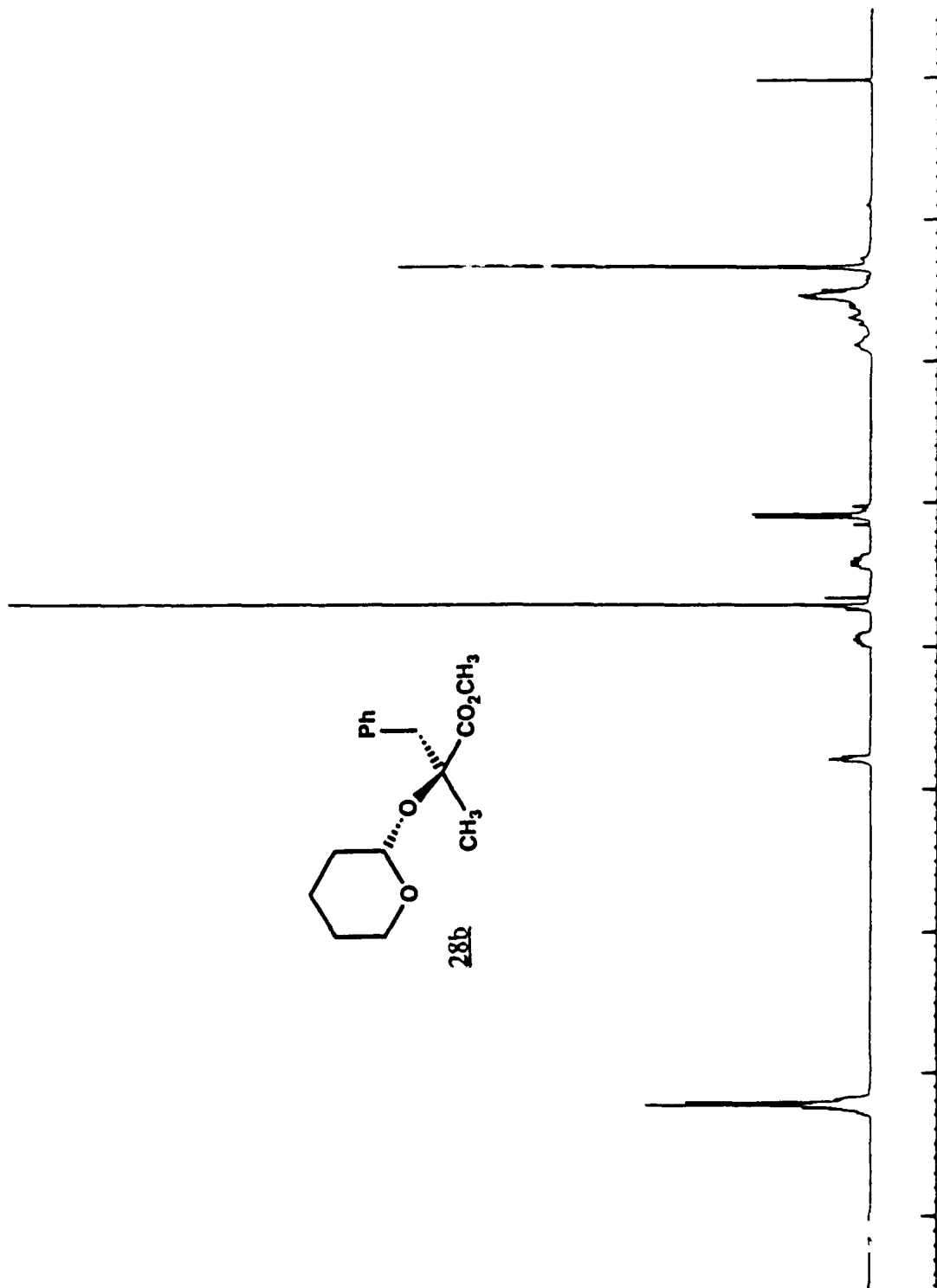
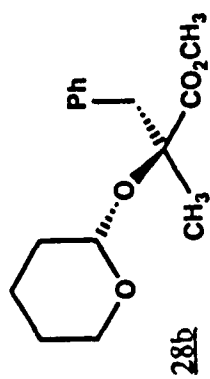


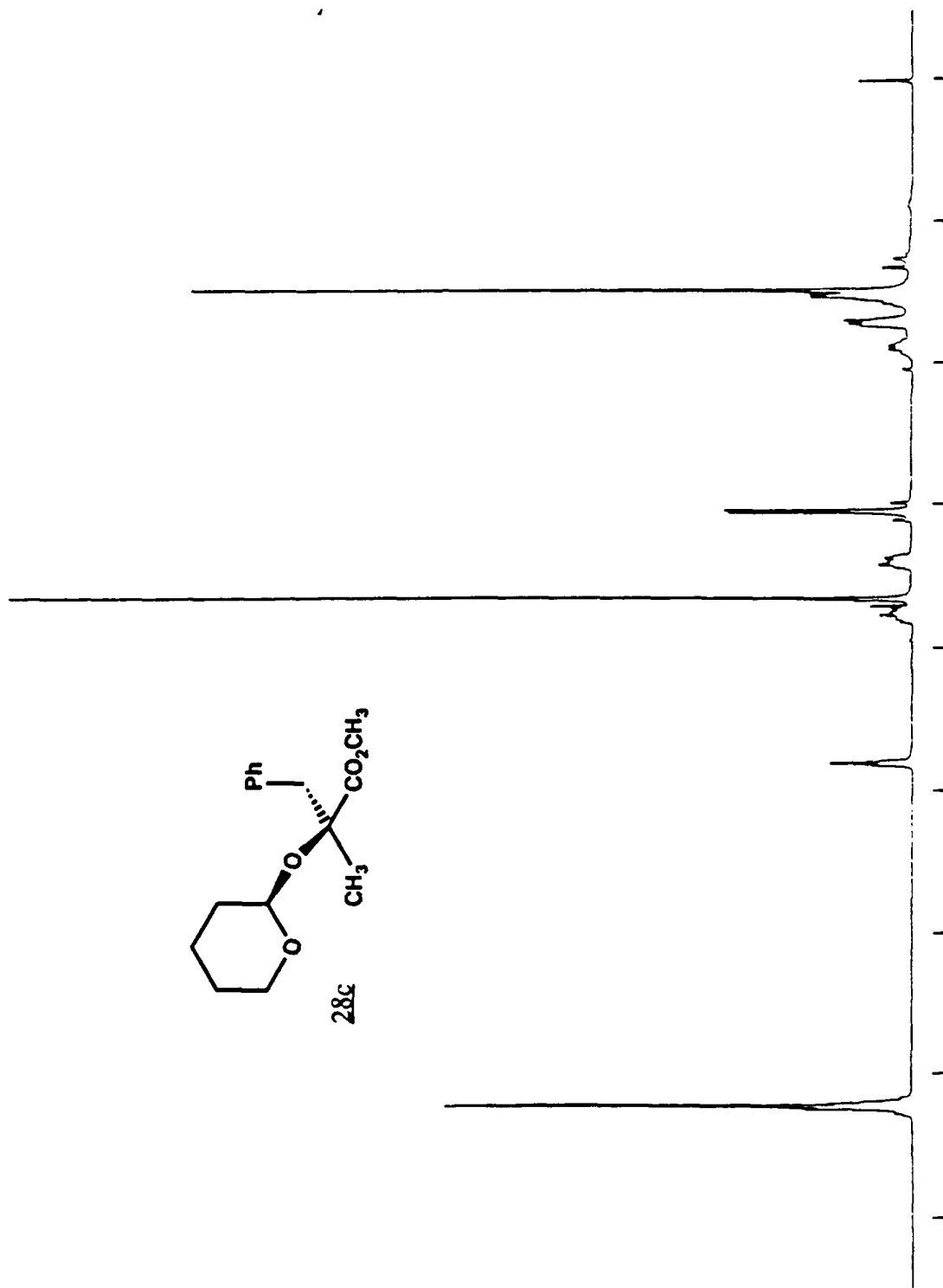
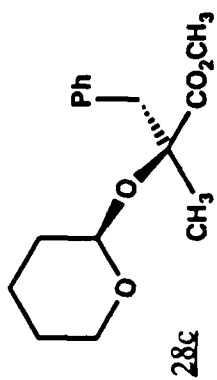


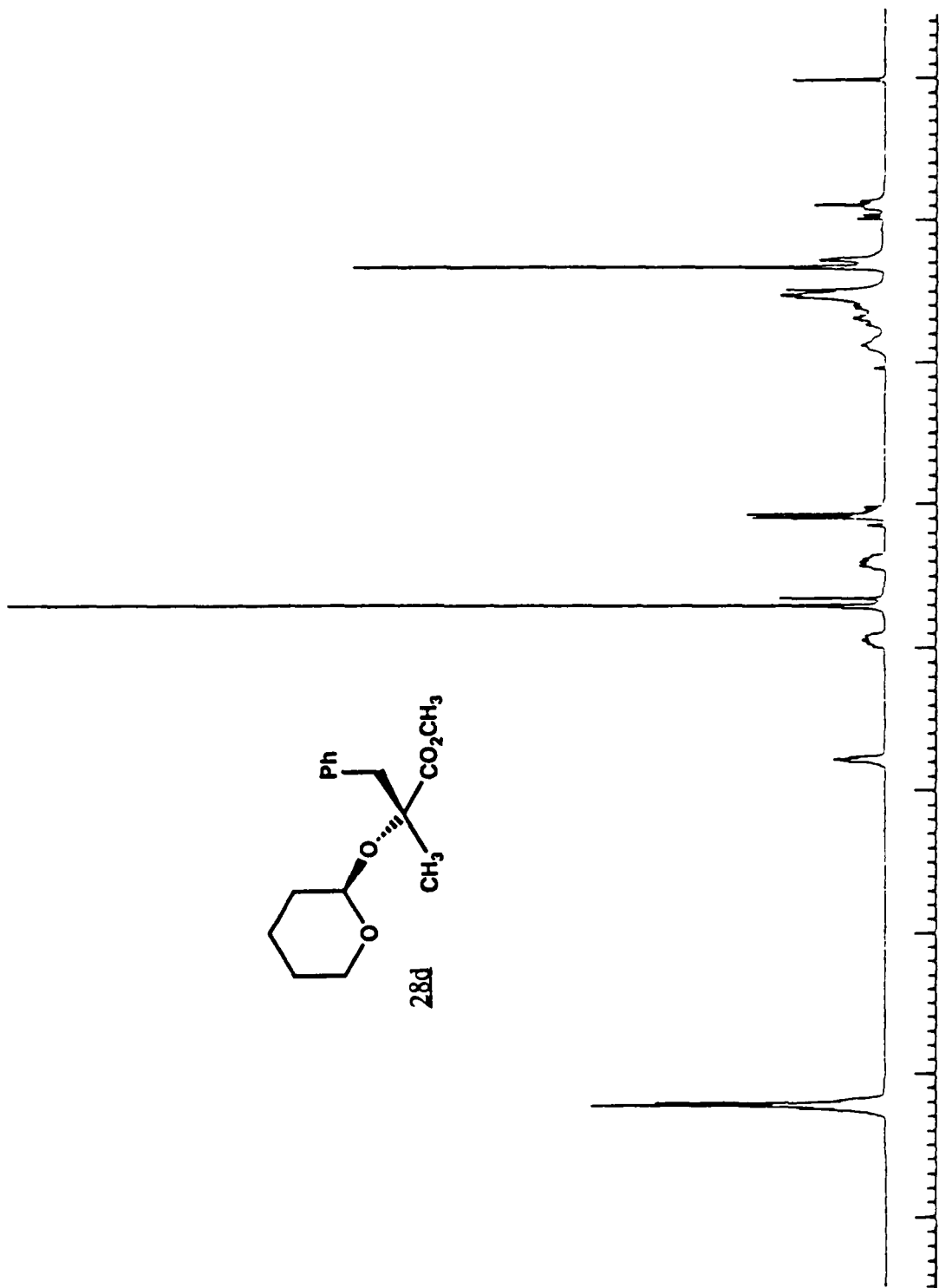
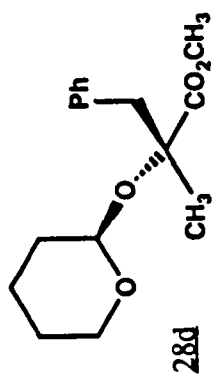


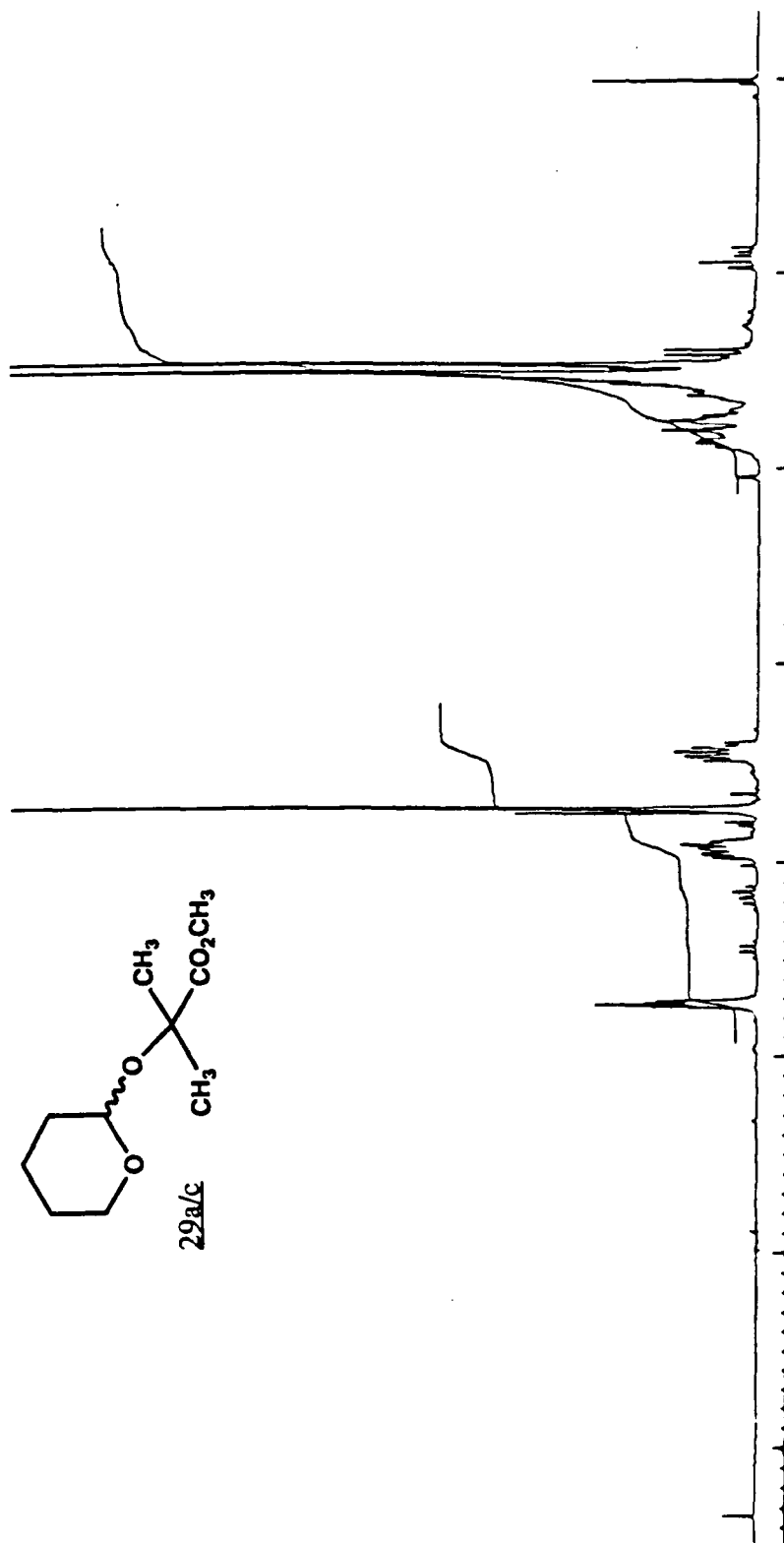
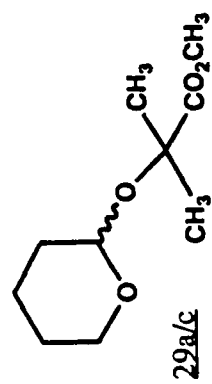


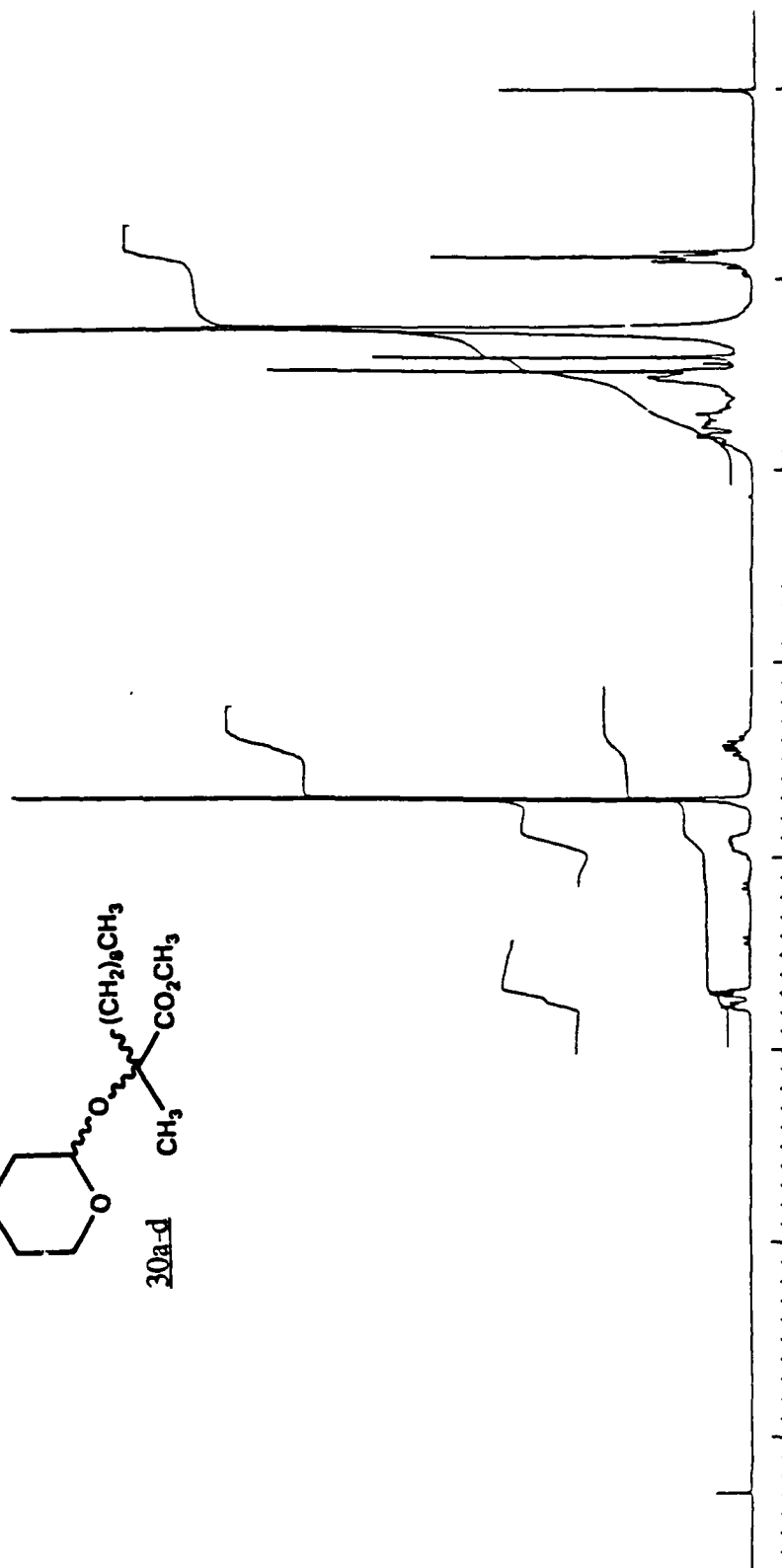
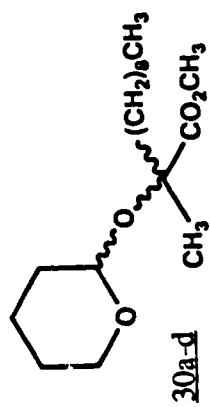


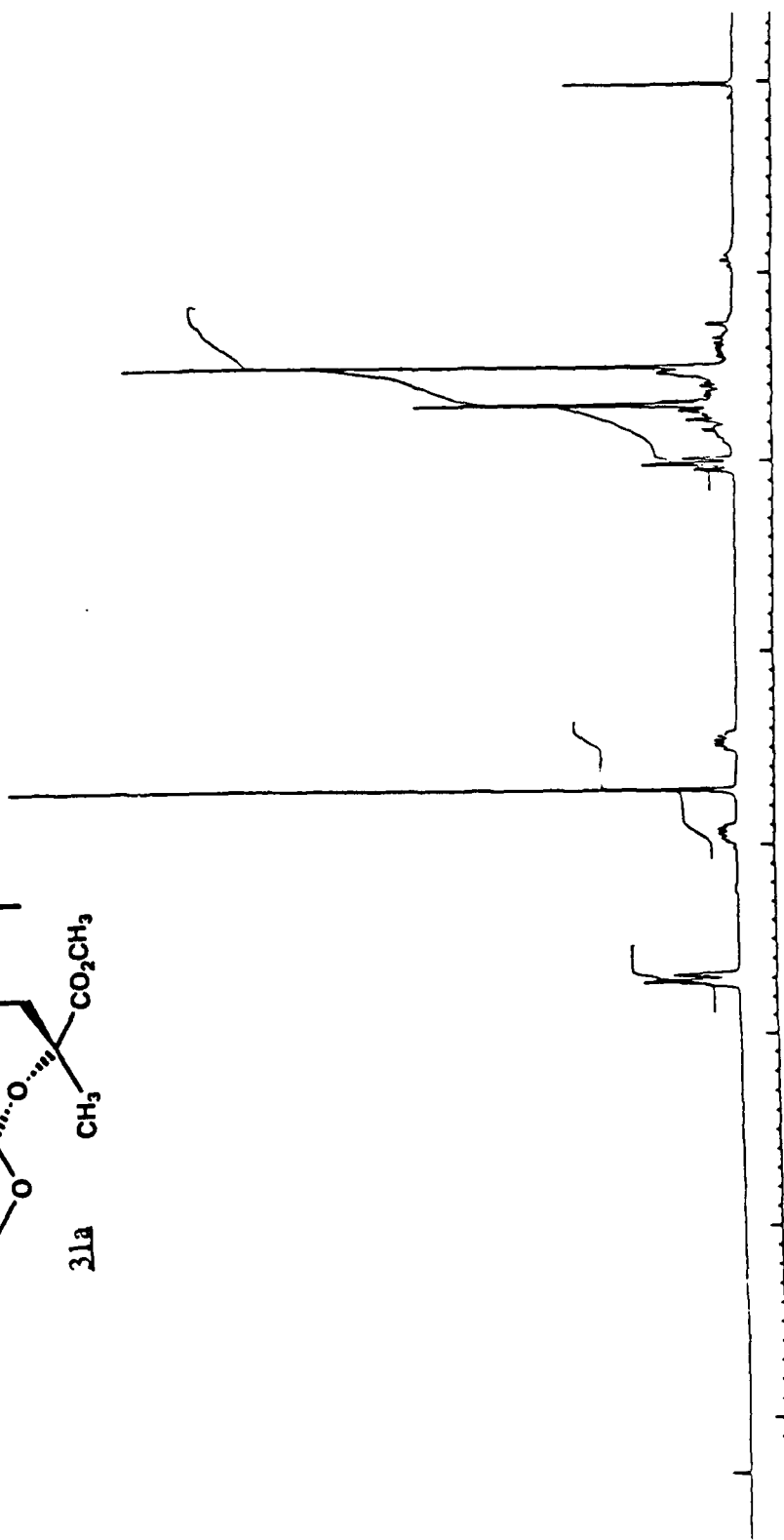
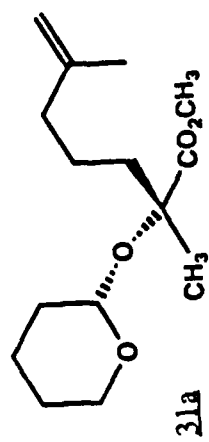


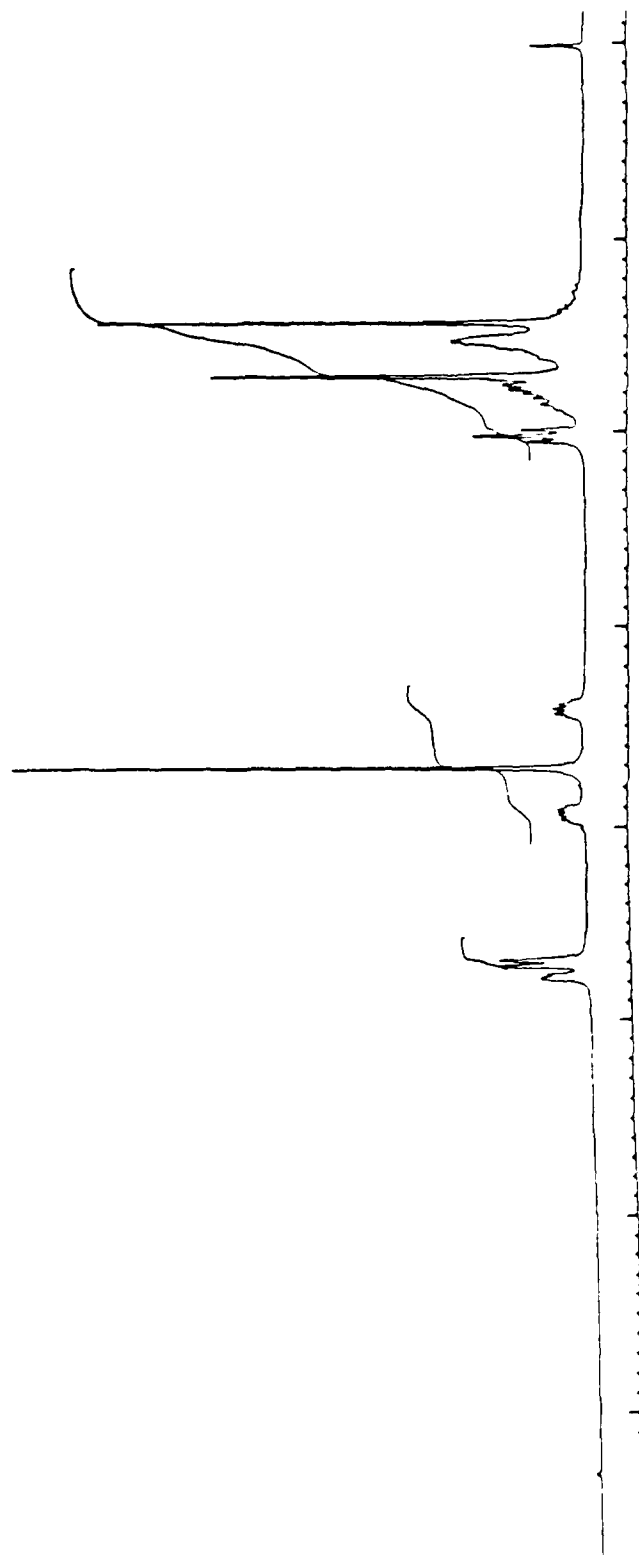
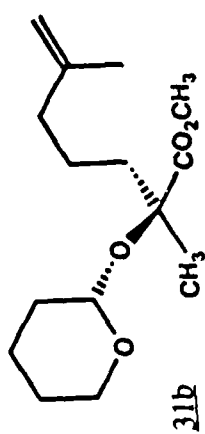




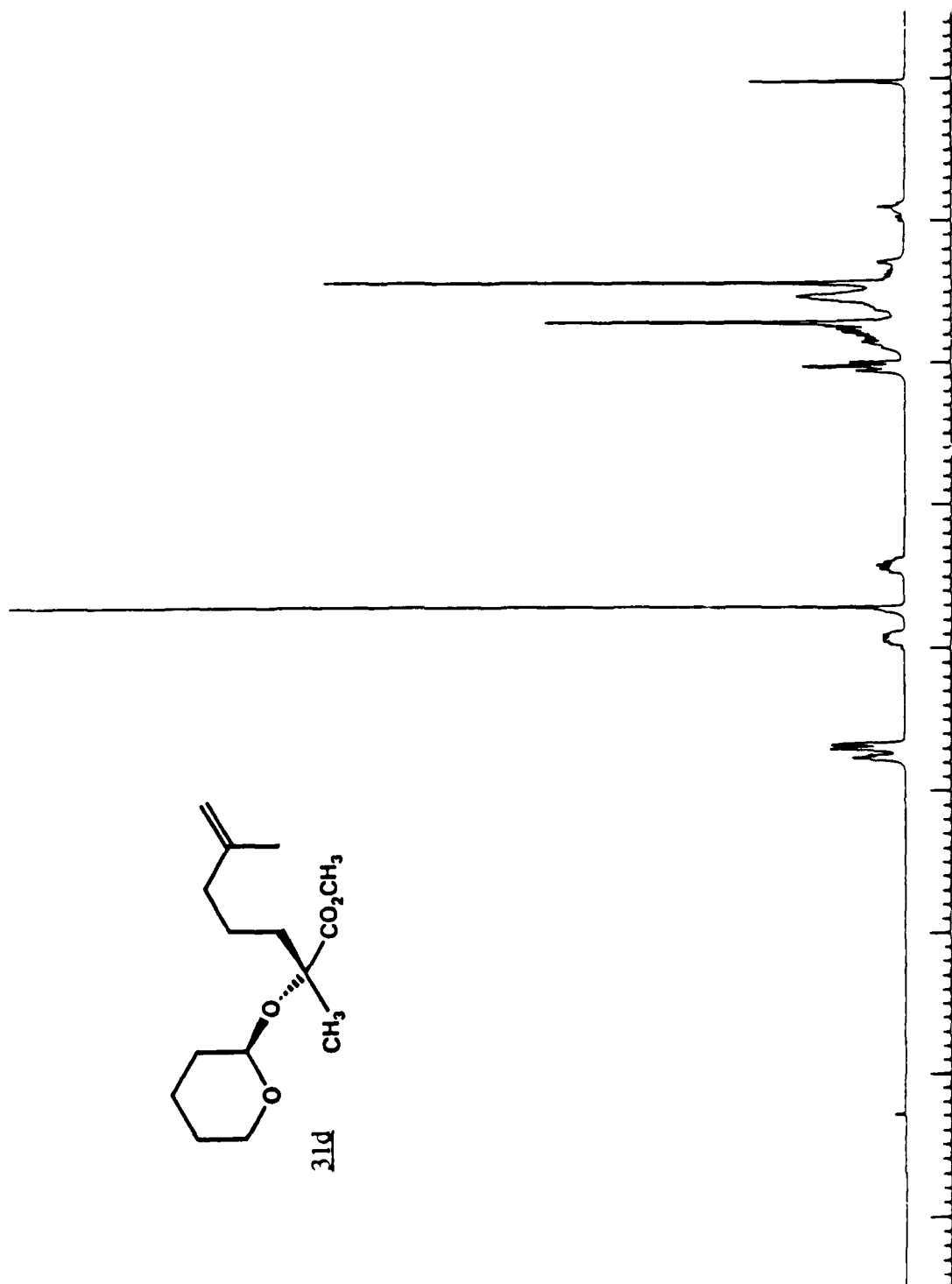


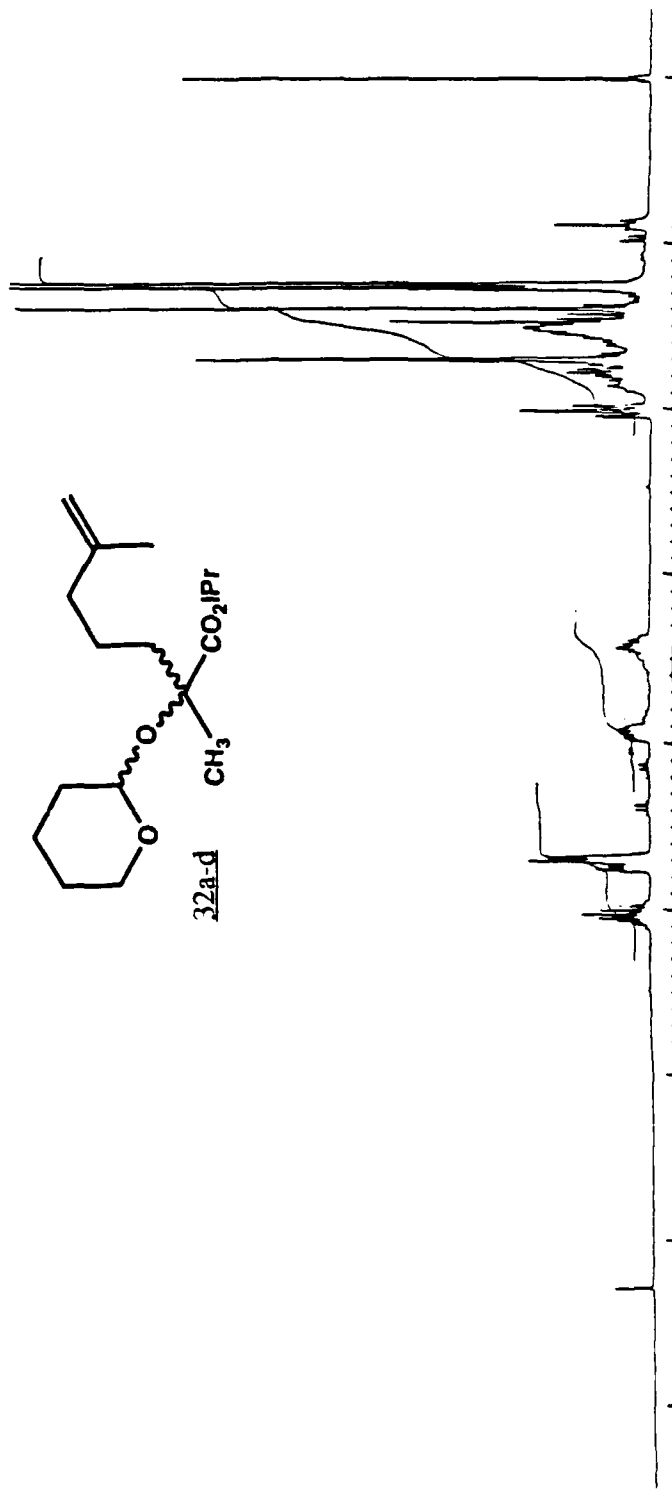
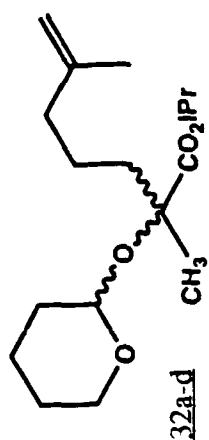


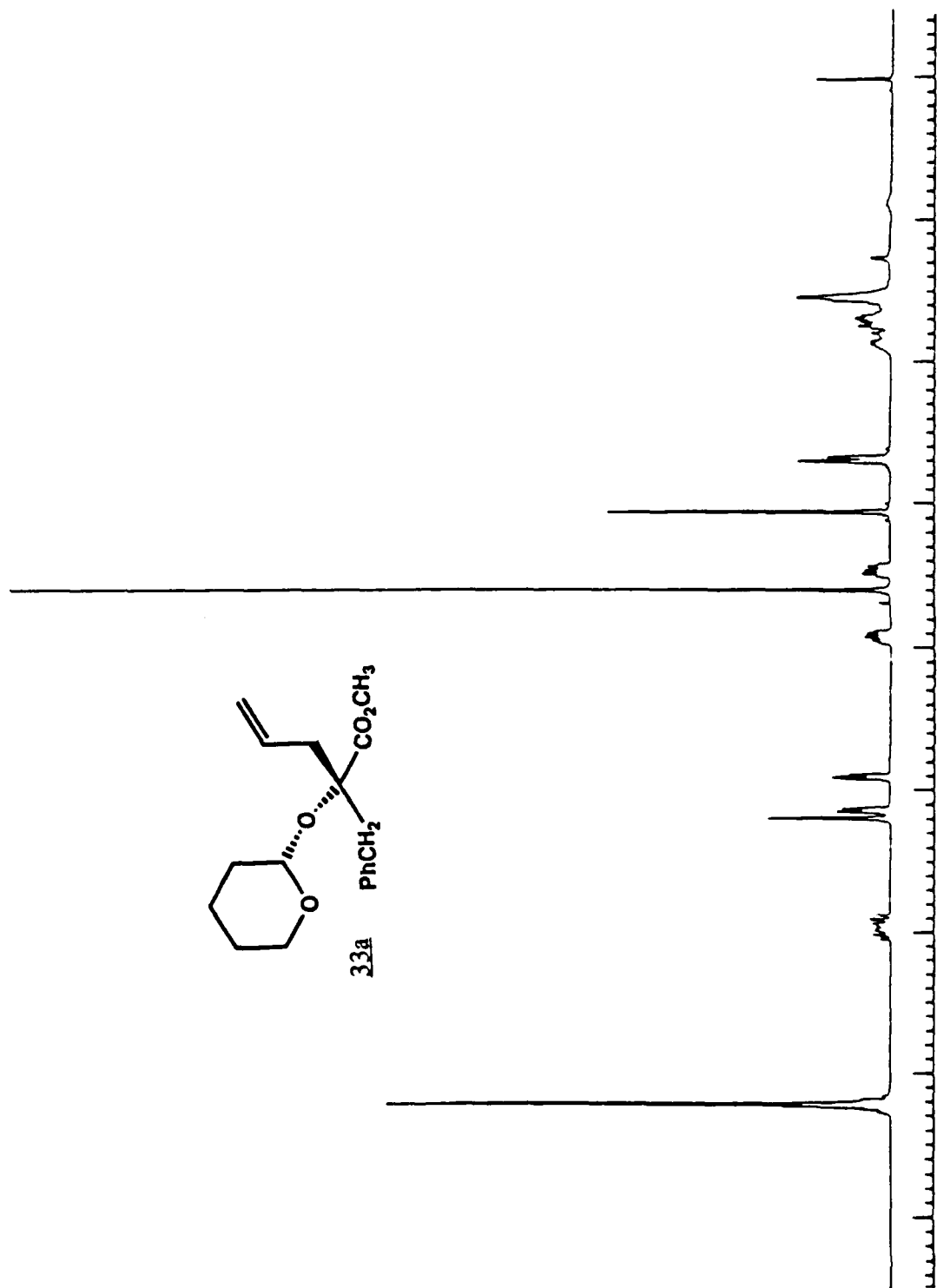
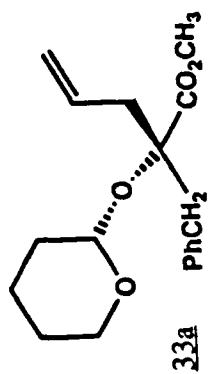


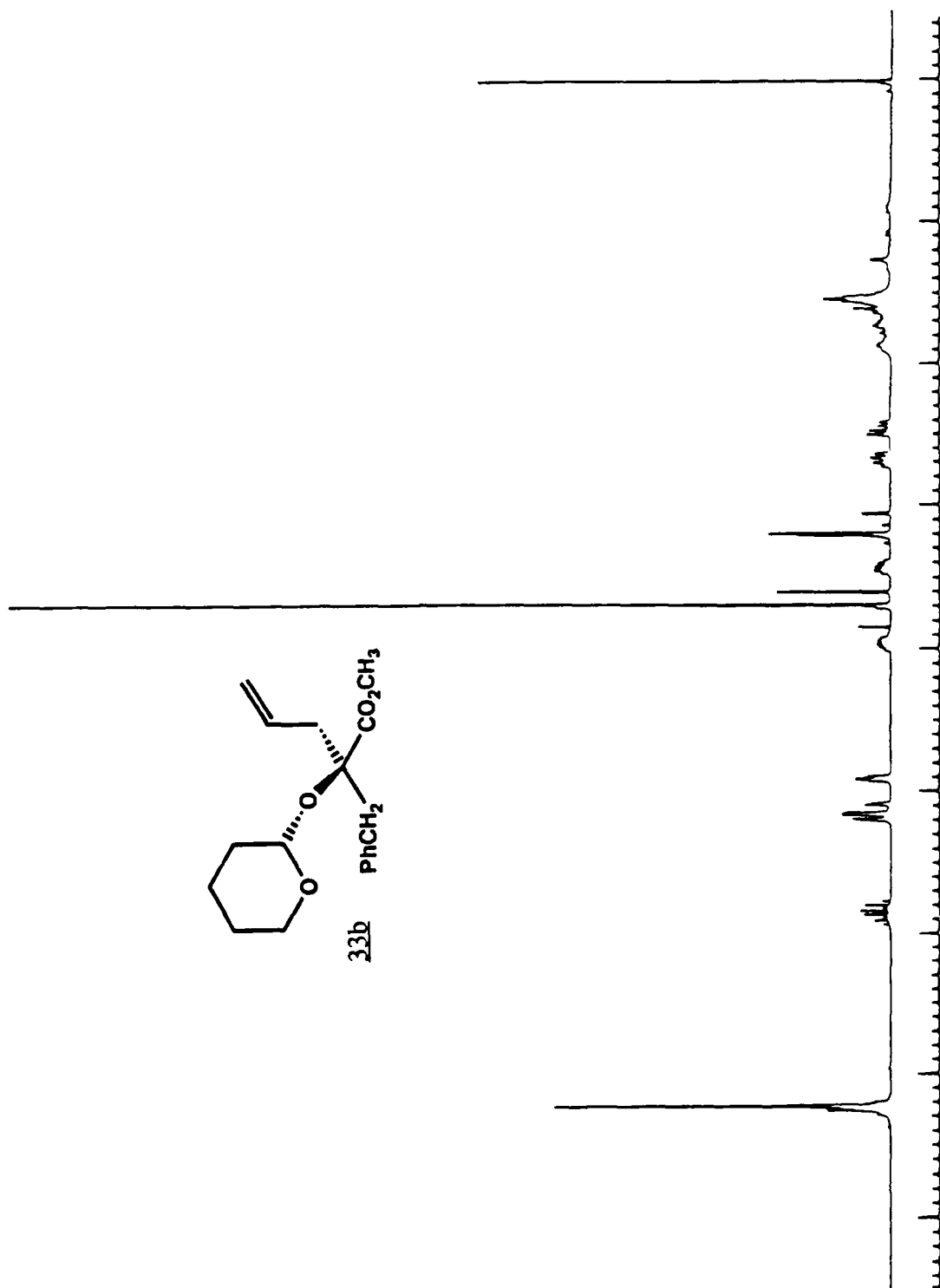
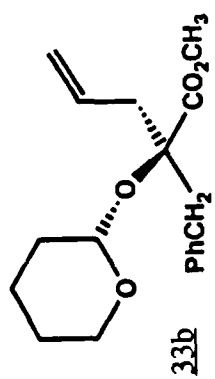


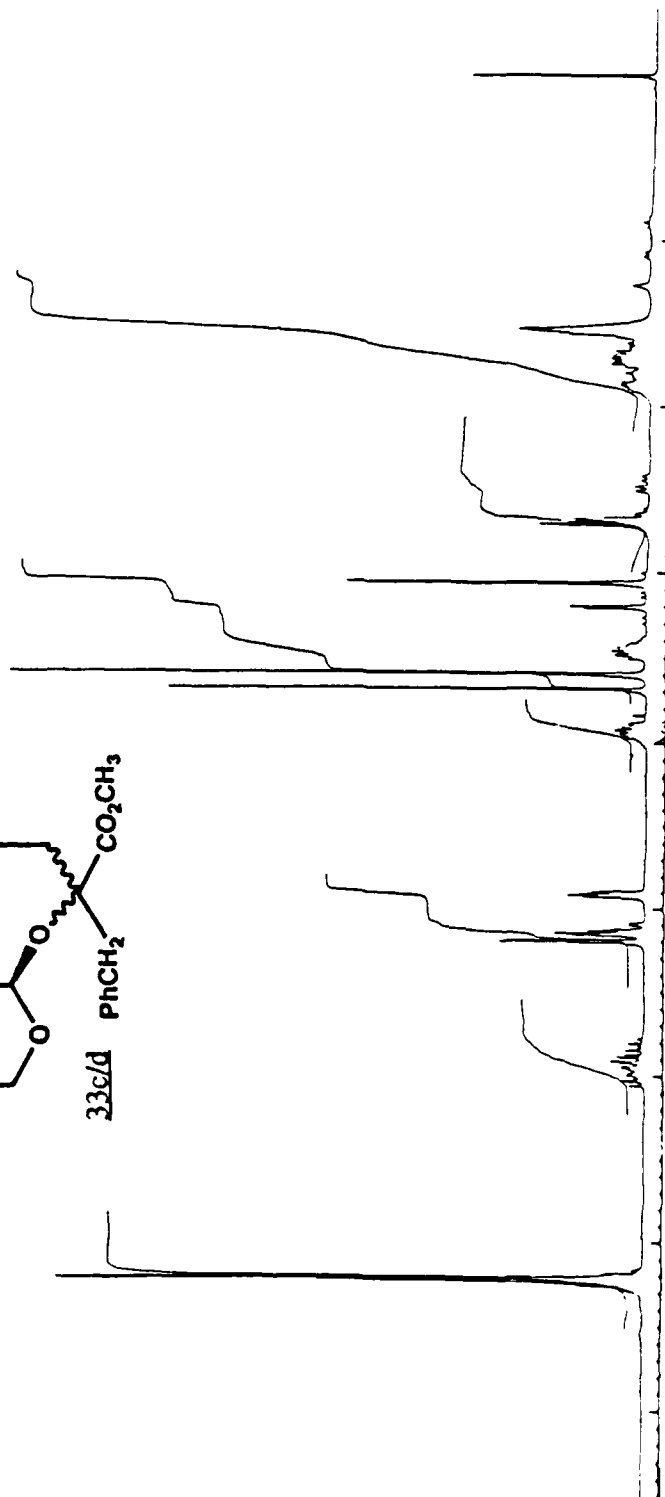
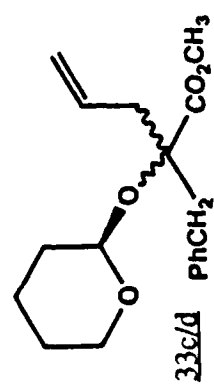


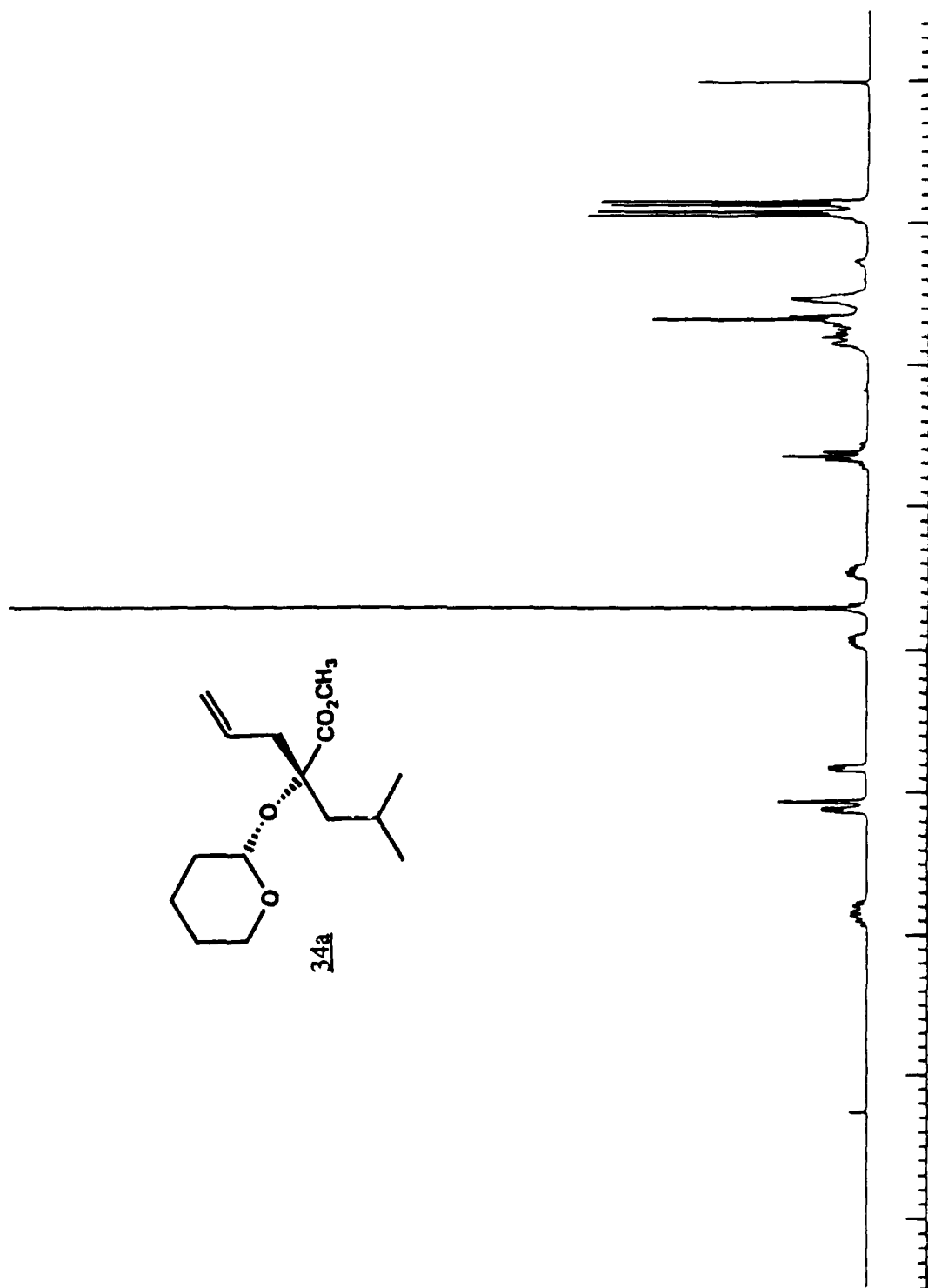


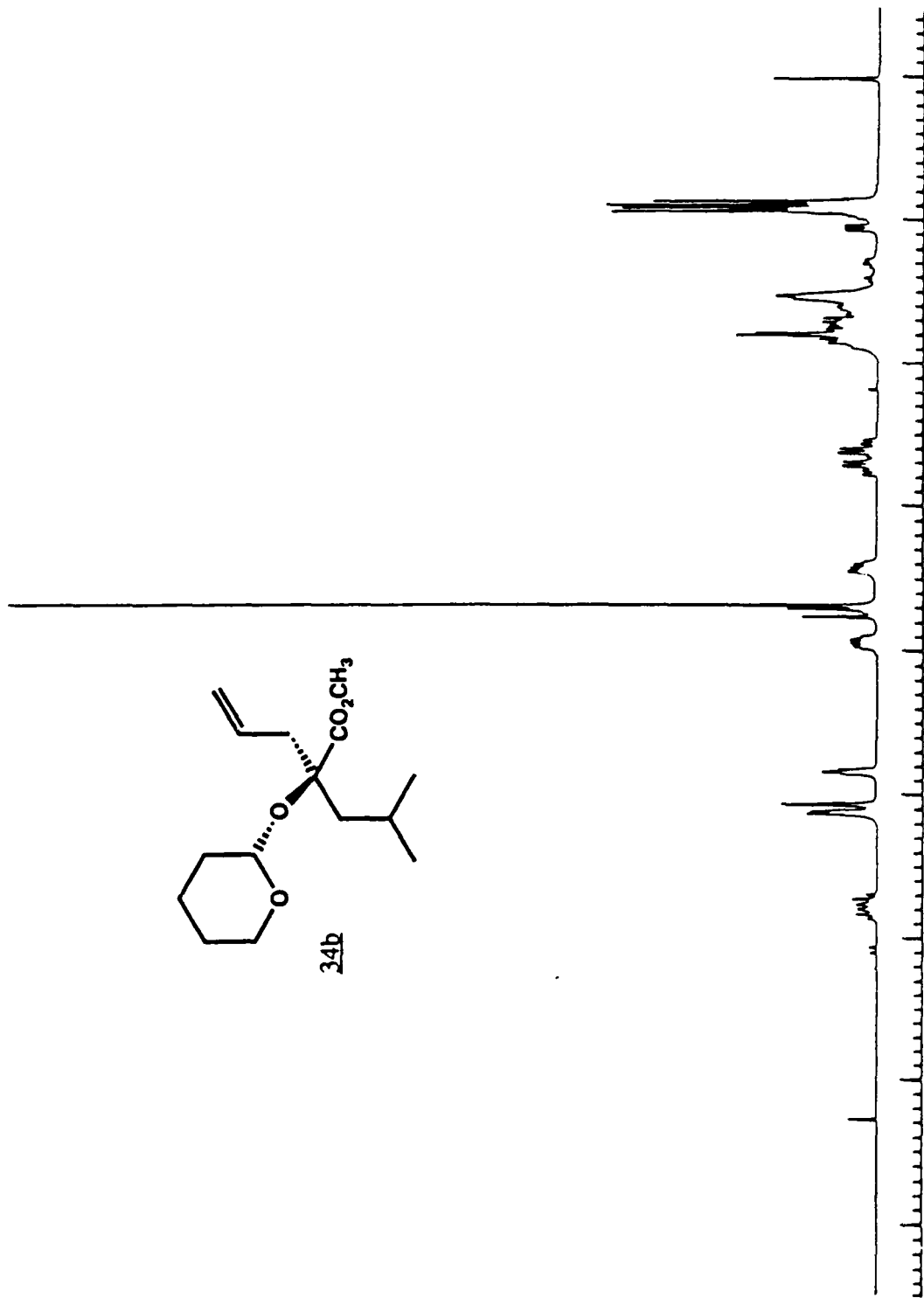
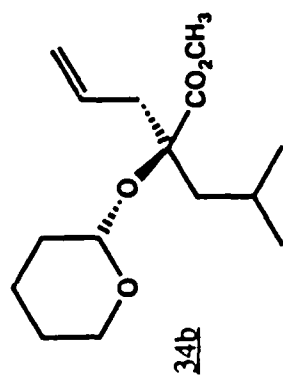


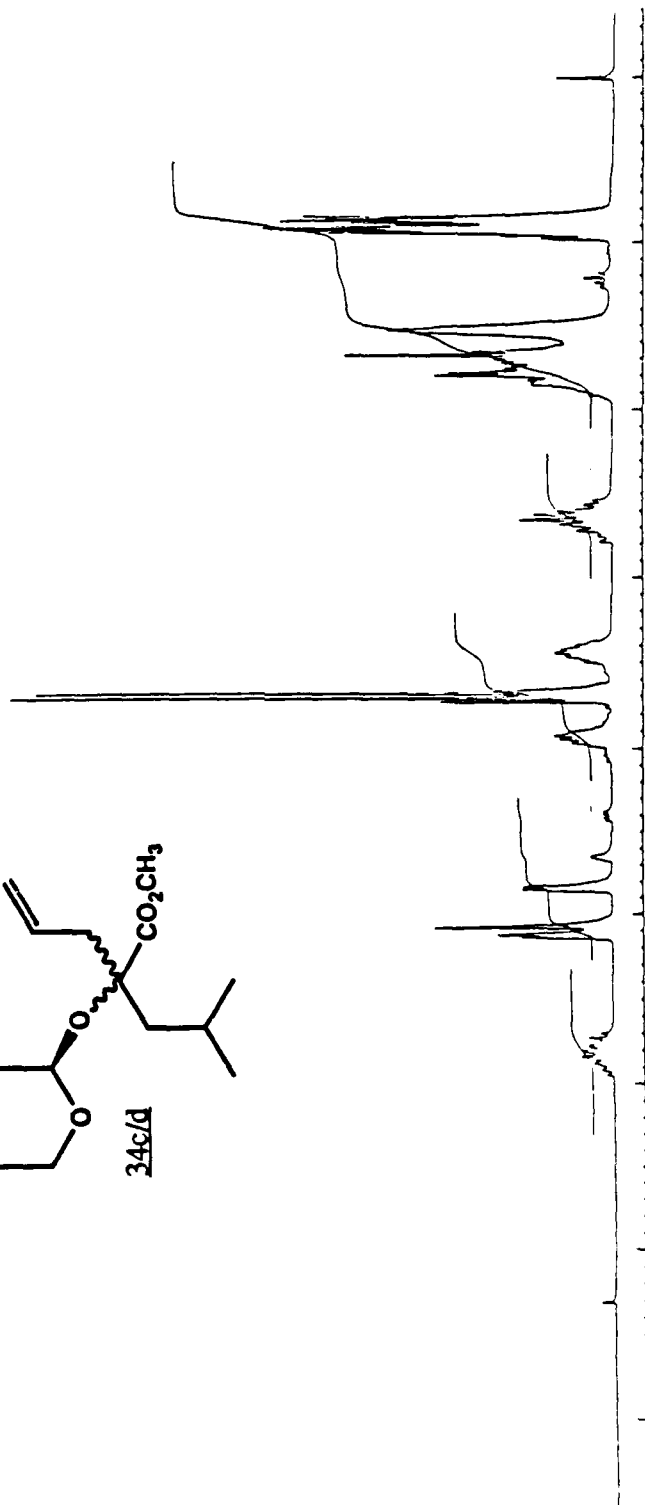
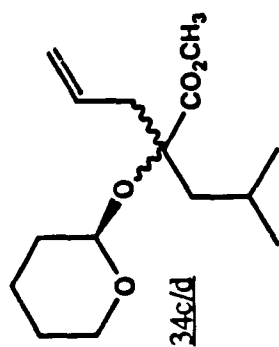


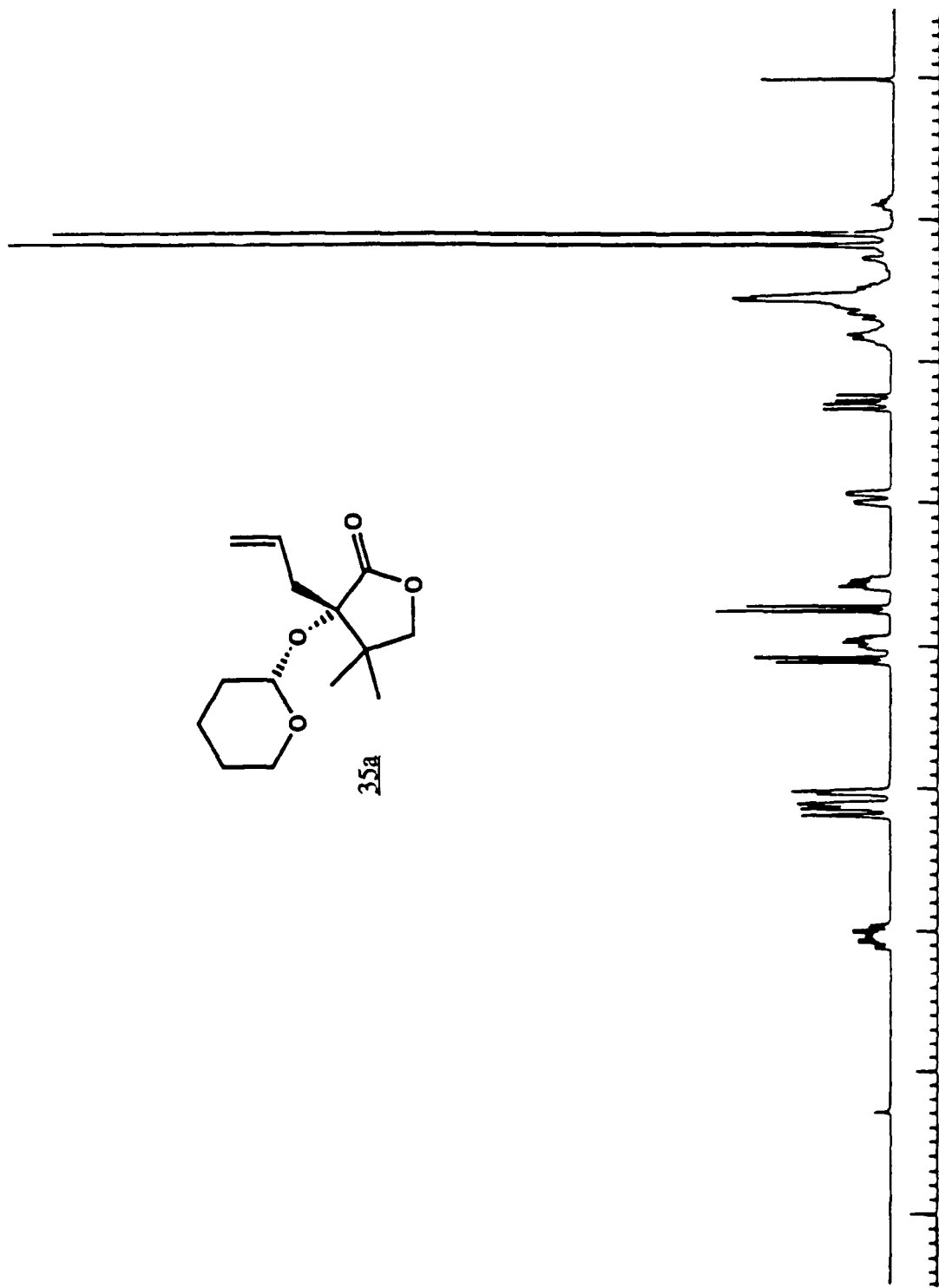
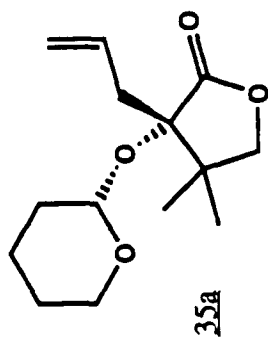


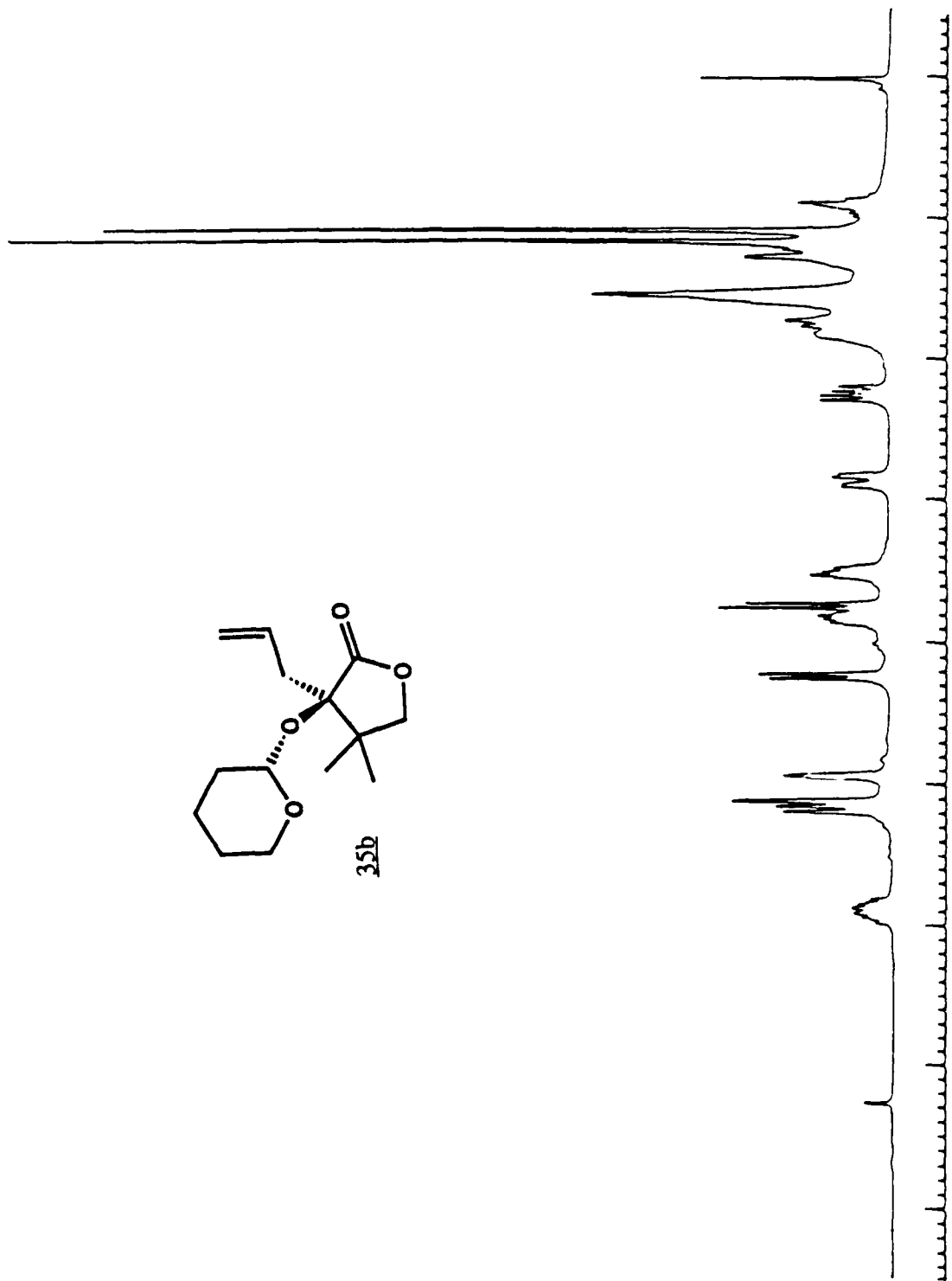
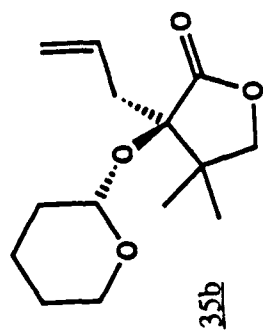


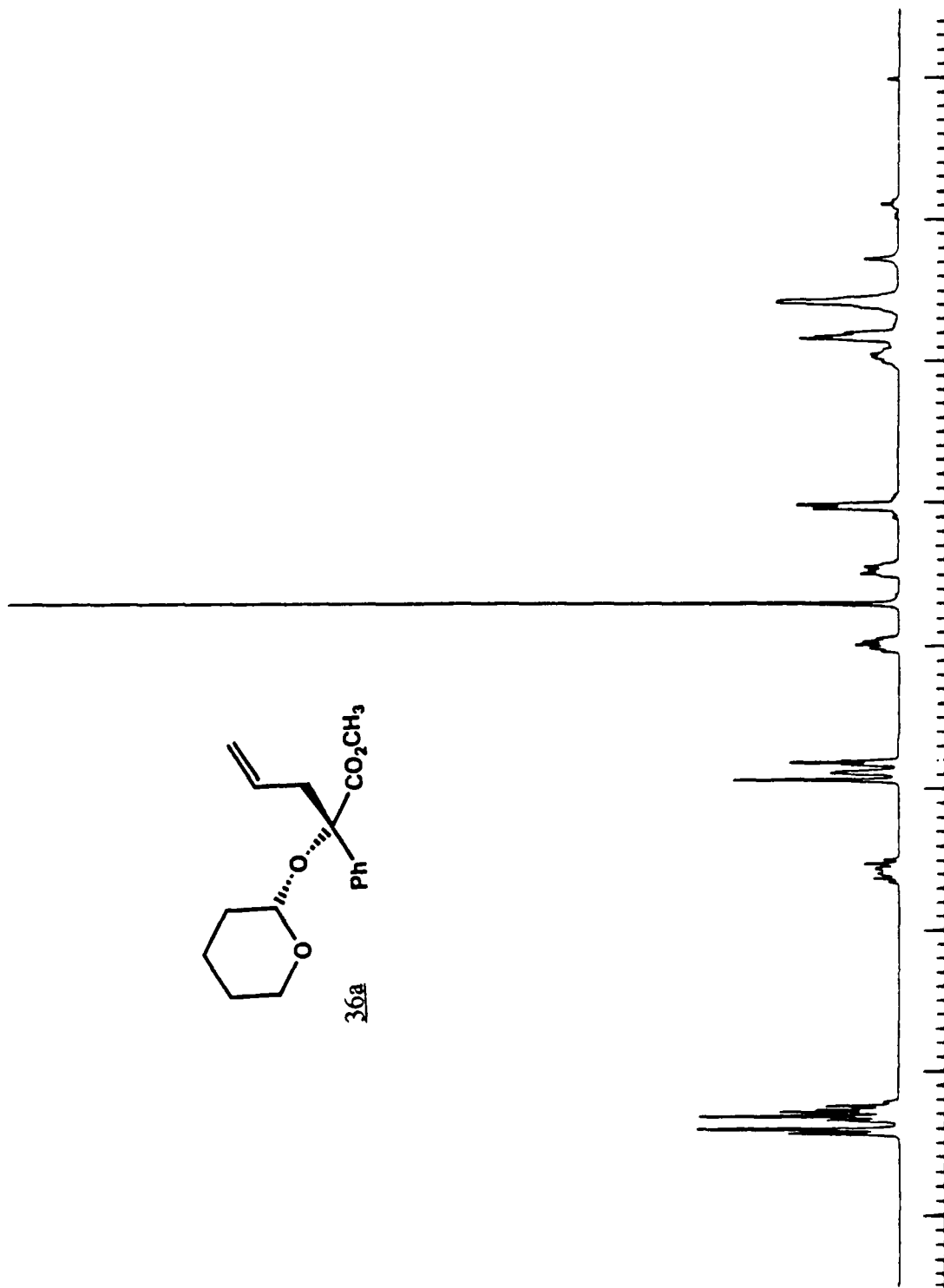
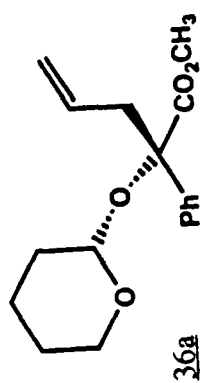


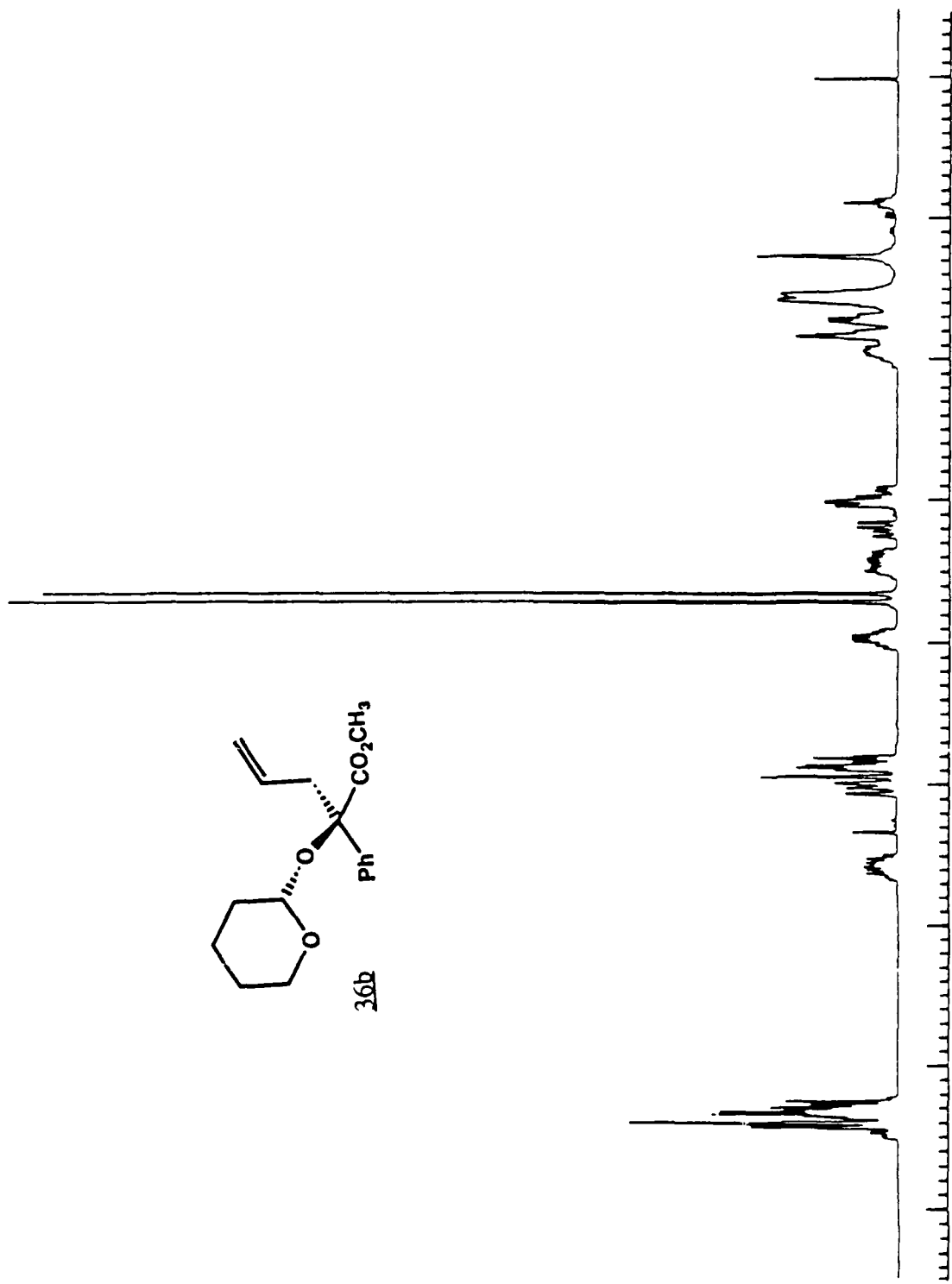
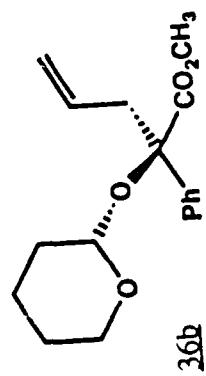


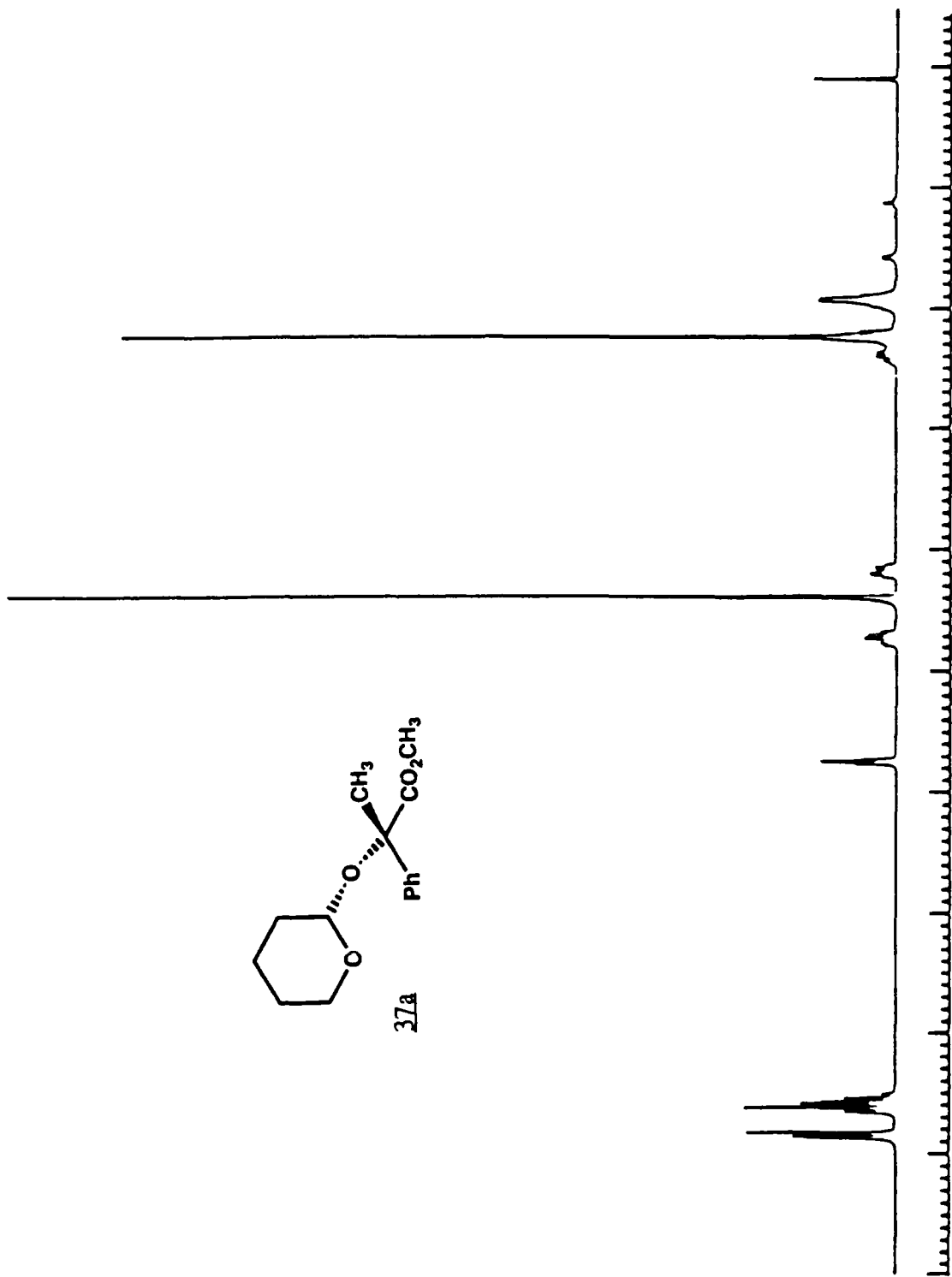
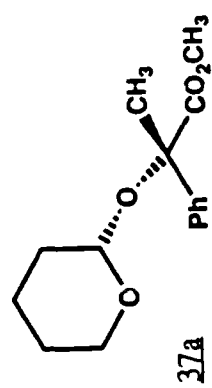


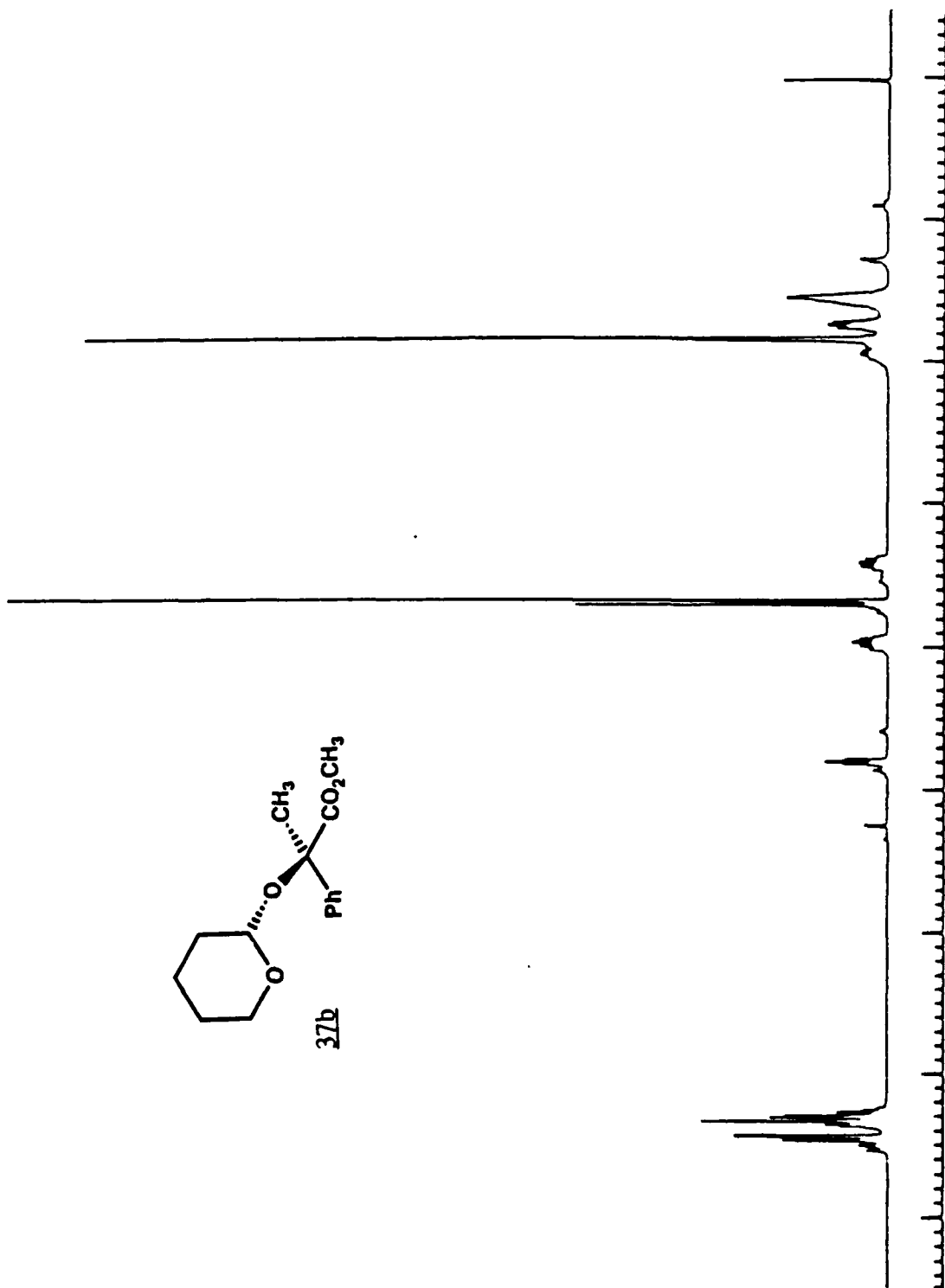
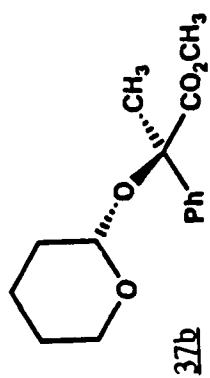


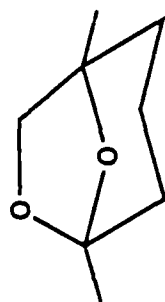




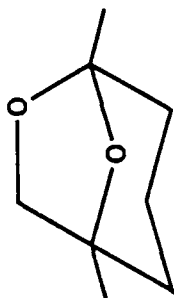




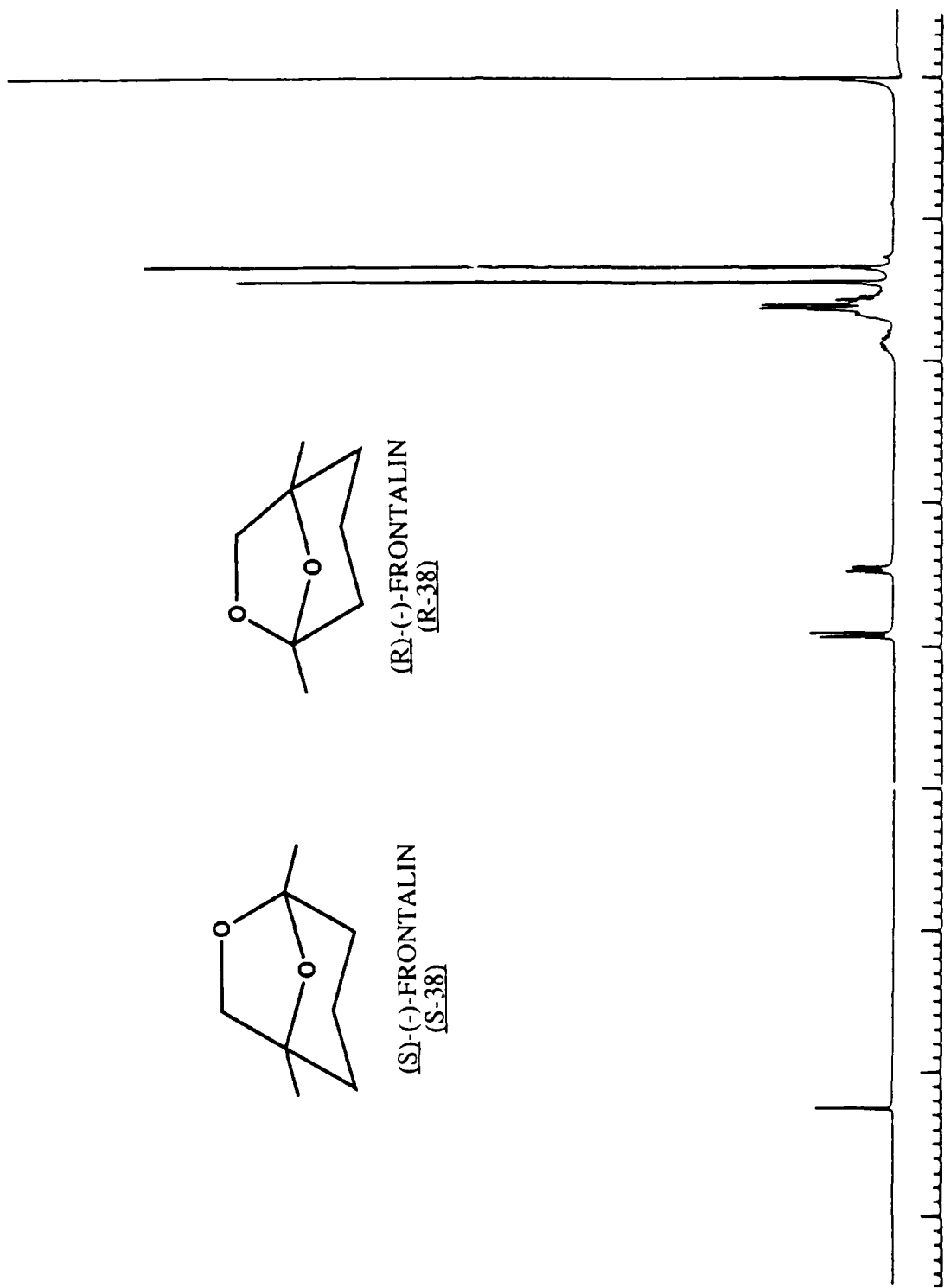


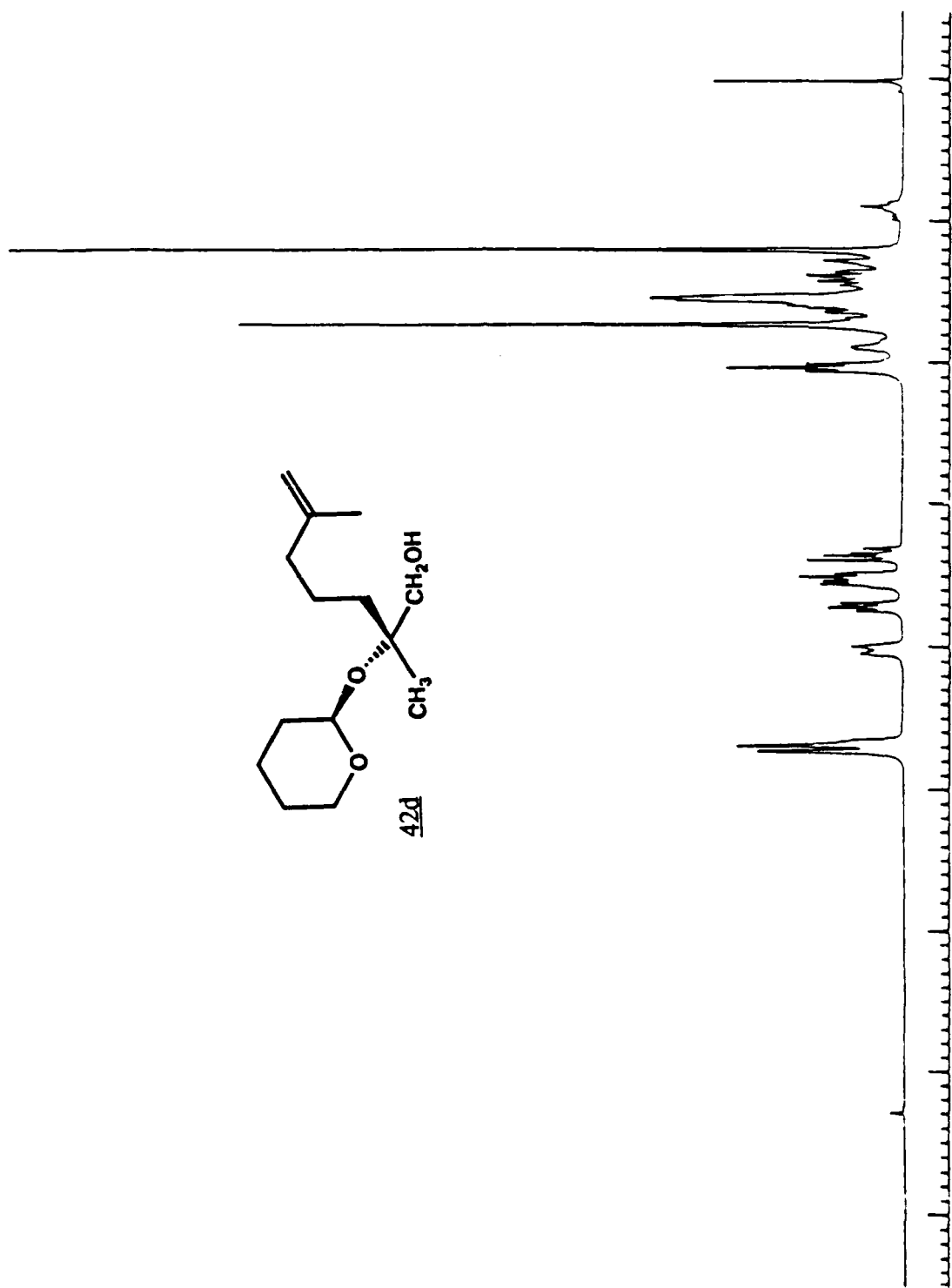
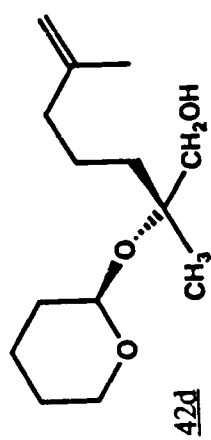


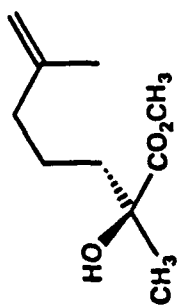
(R)-(-)-FRONTALIN
(R-38)



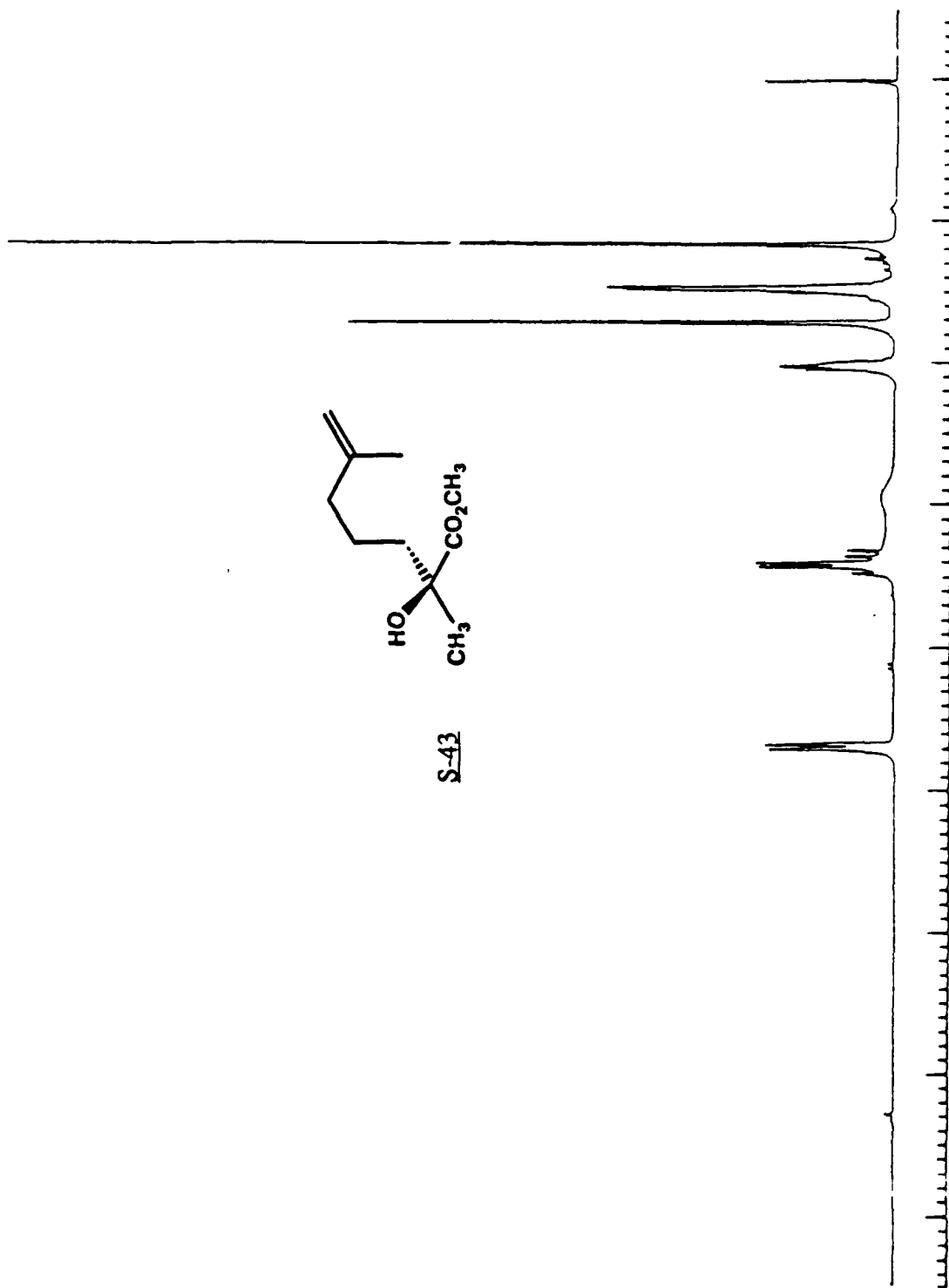
(S)-(-)-FRONTALIN
(S-38)

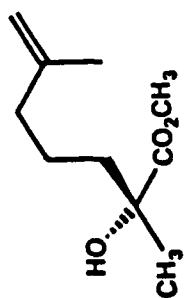




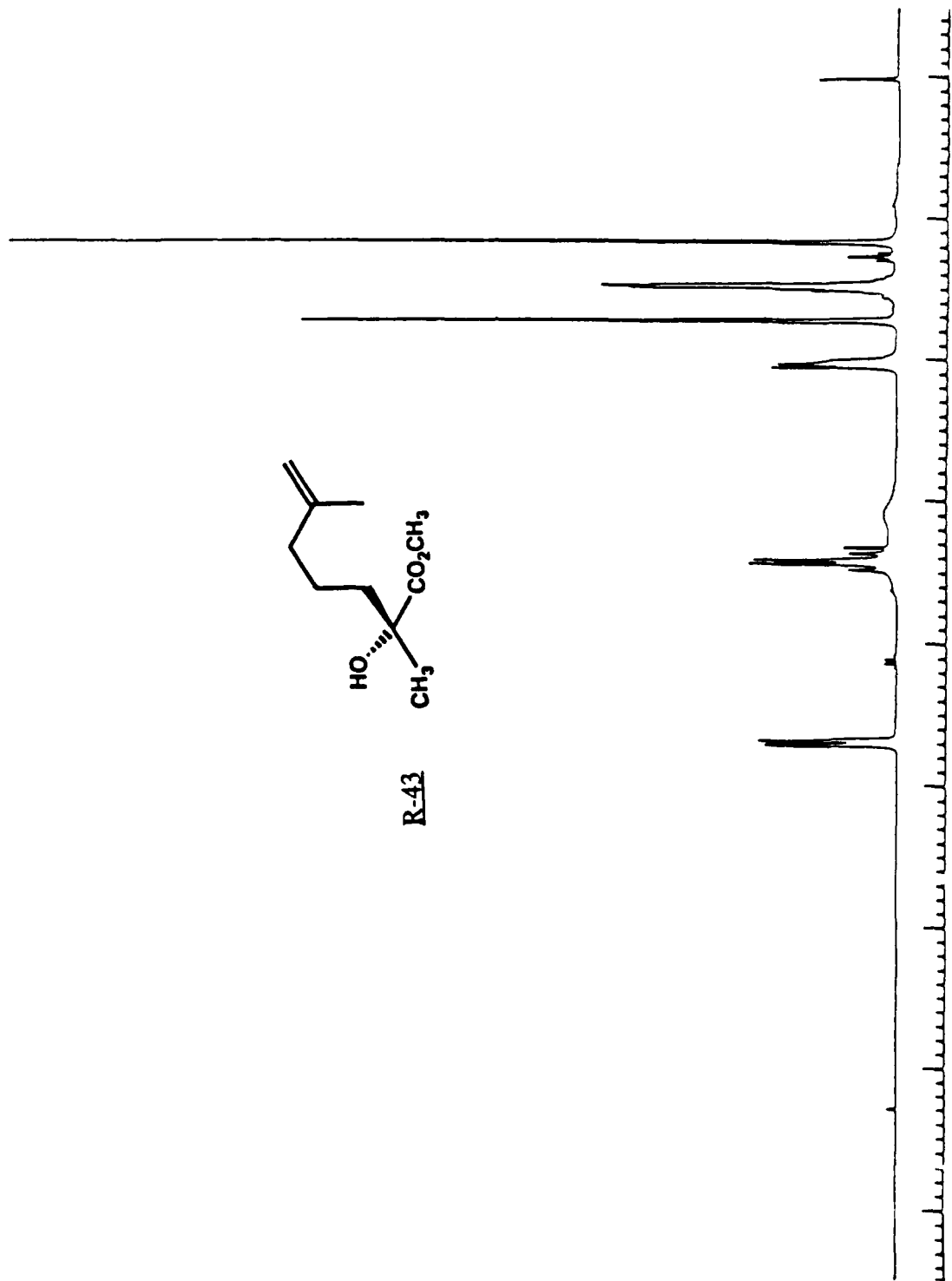


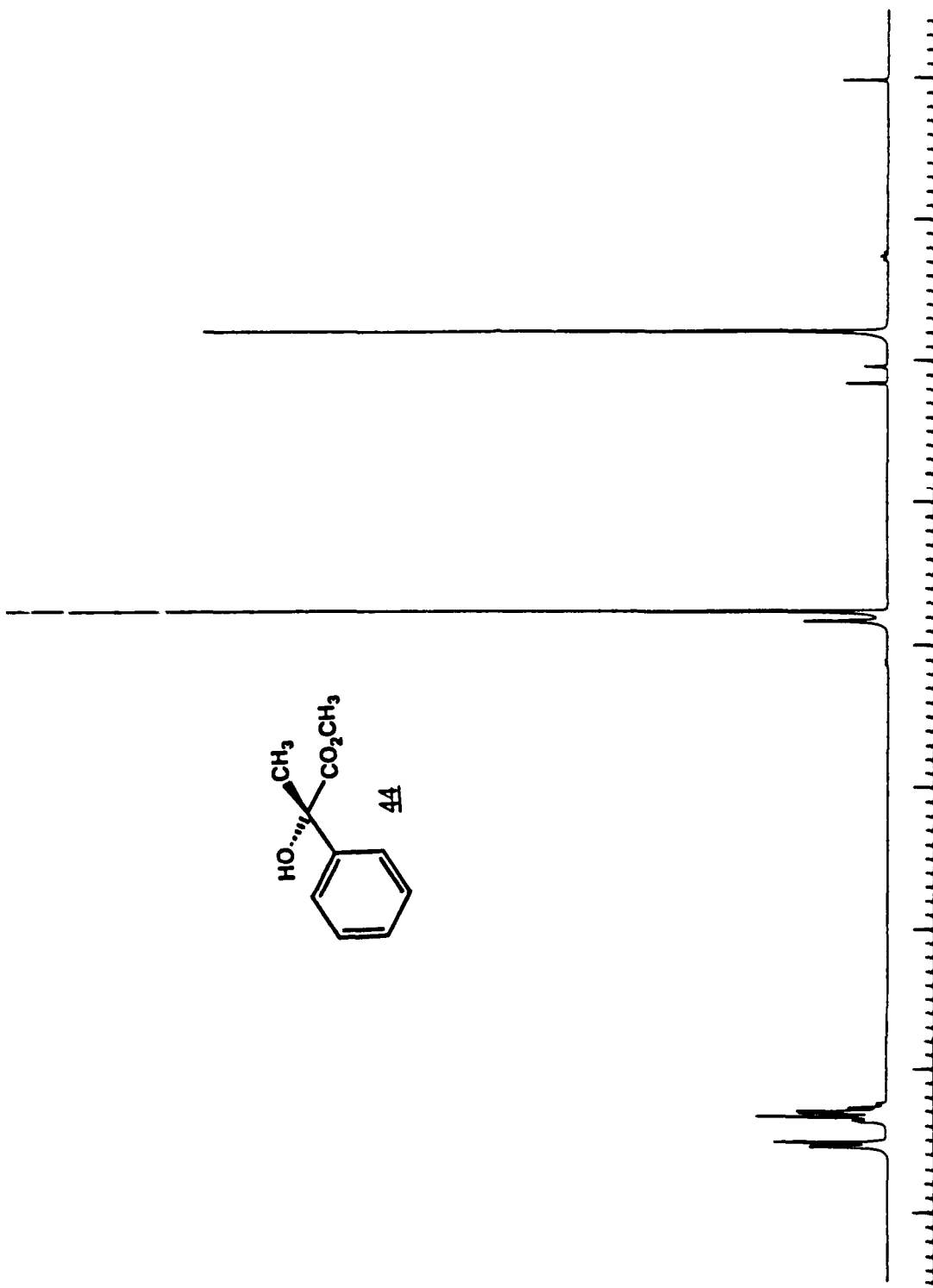
S-43

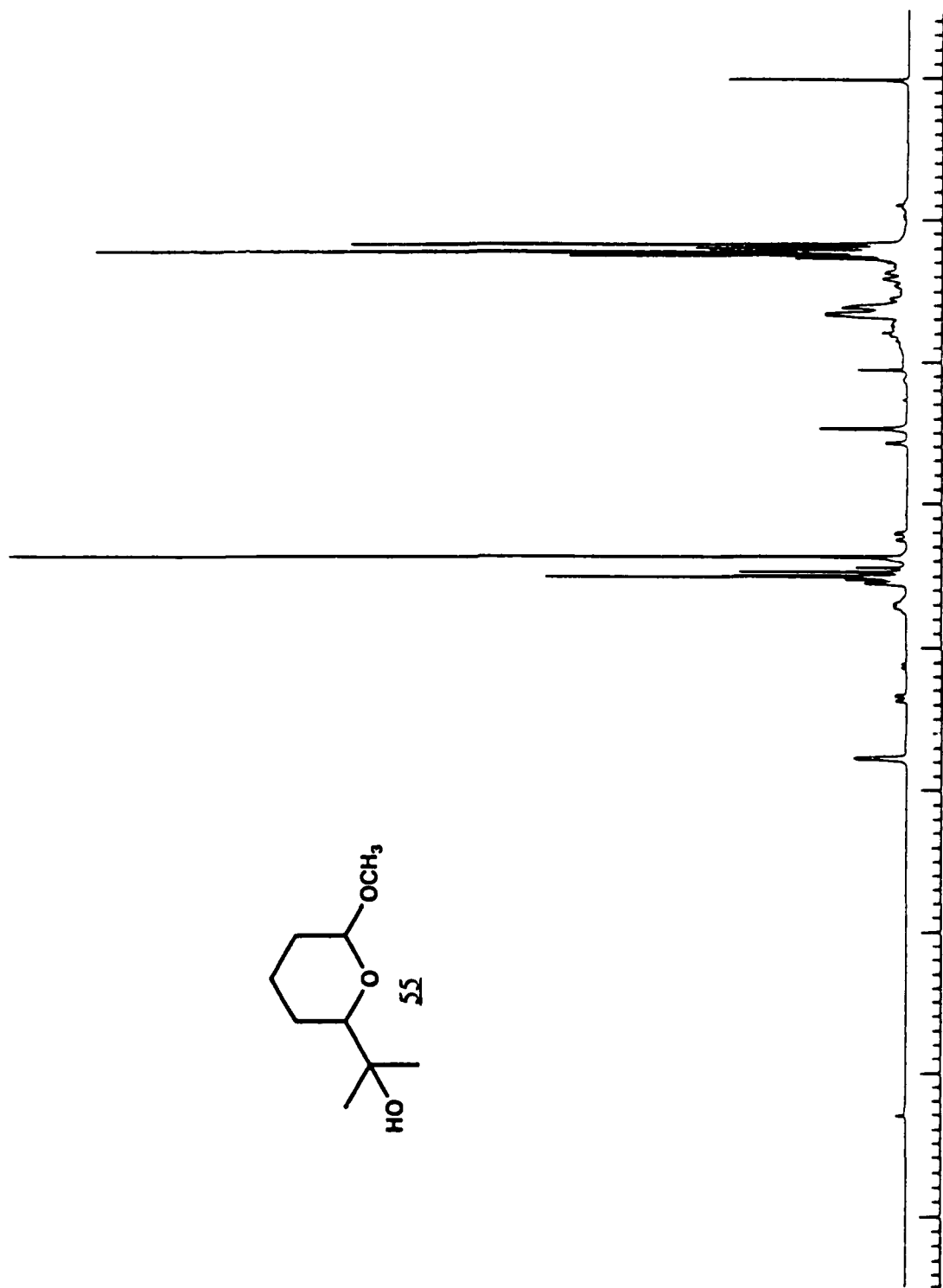


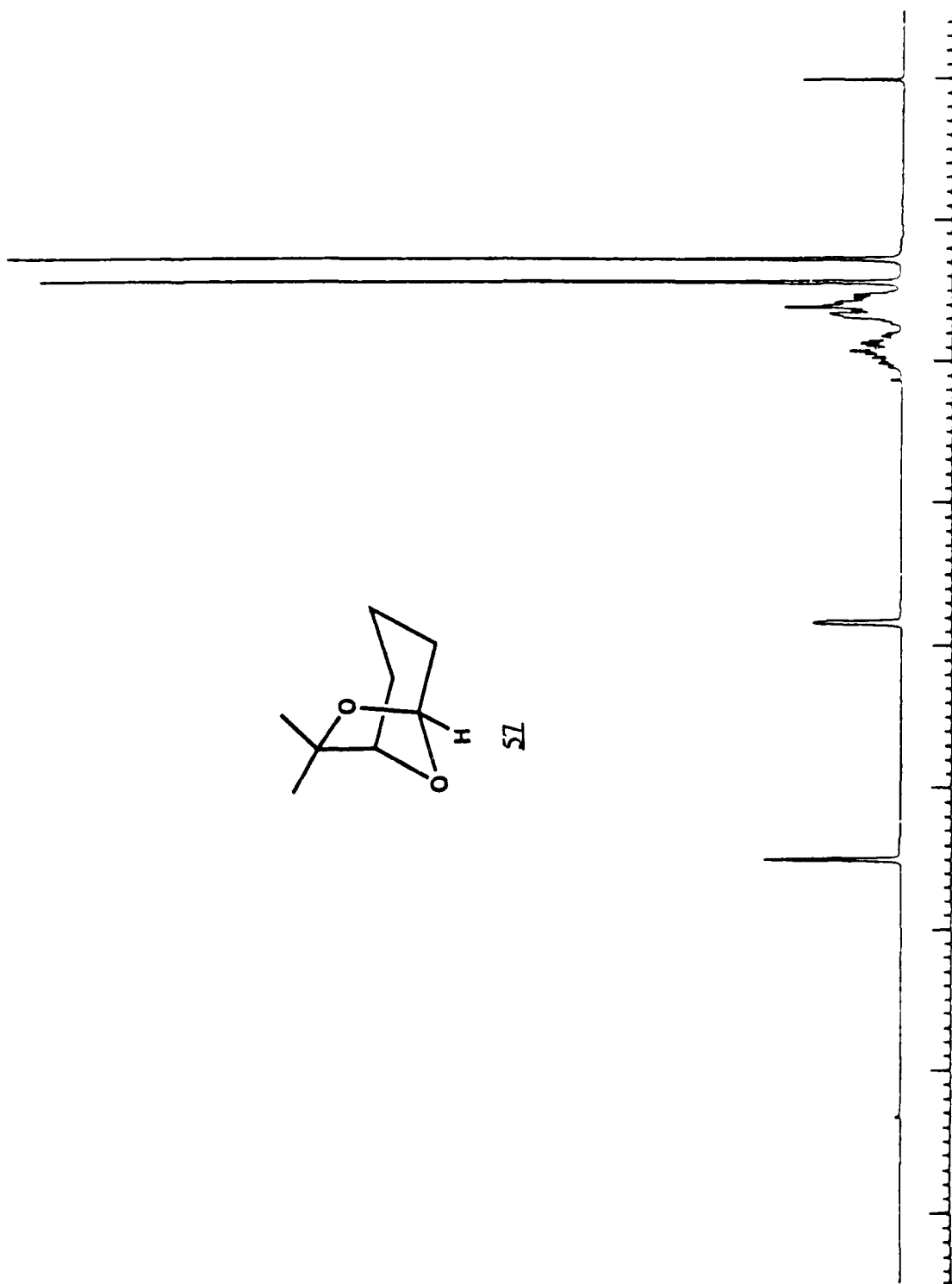


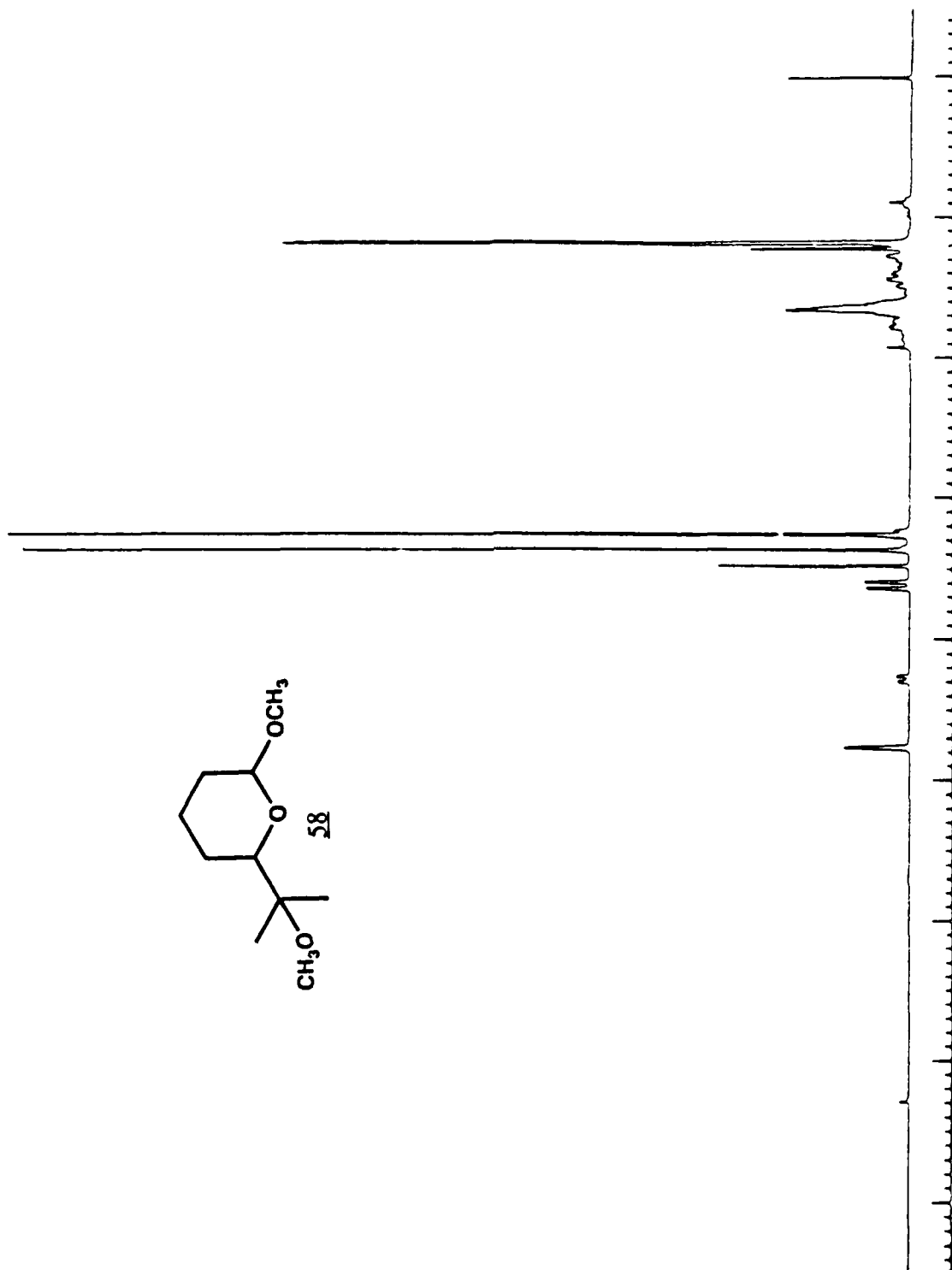
R-43

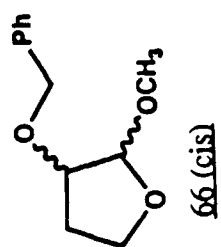


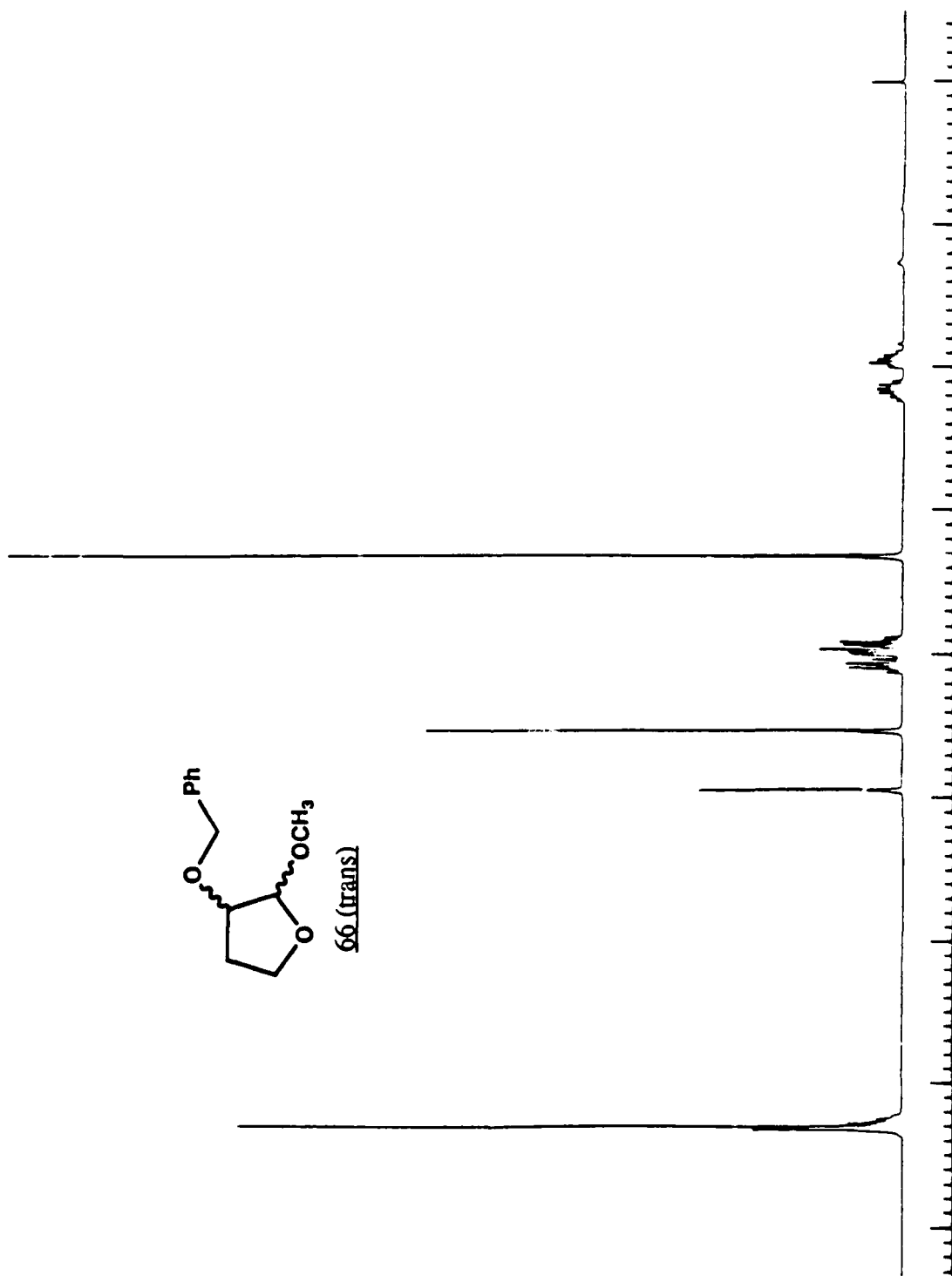


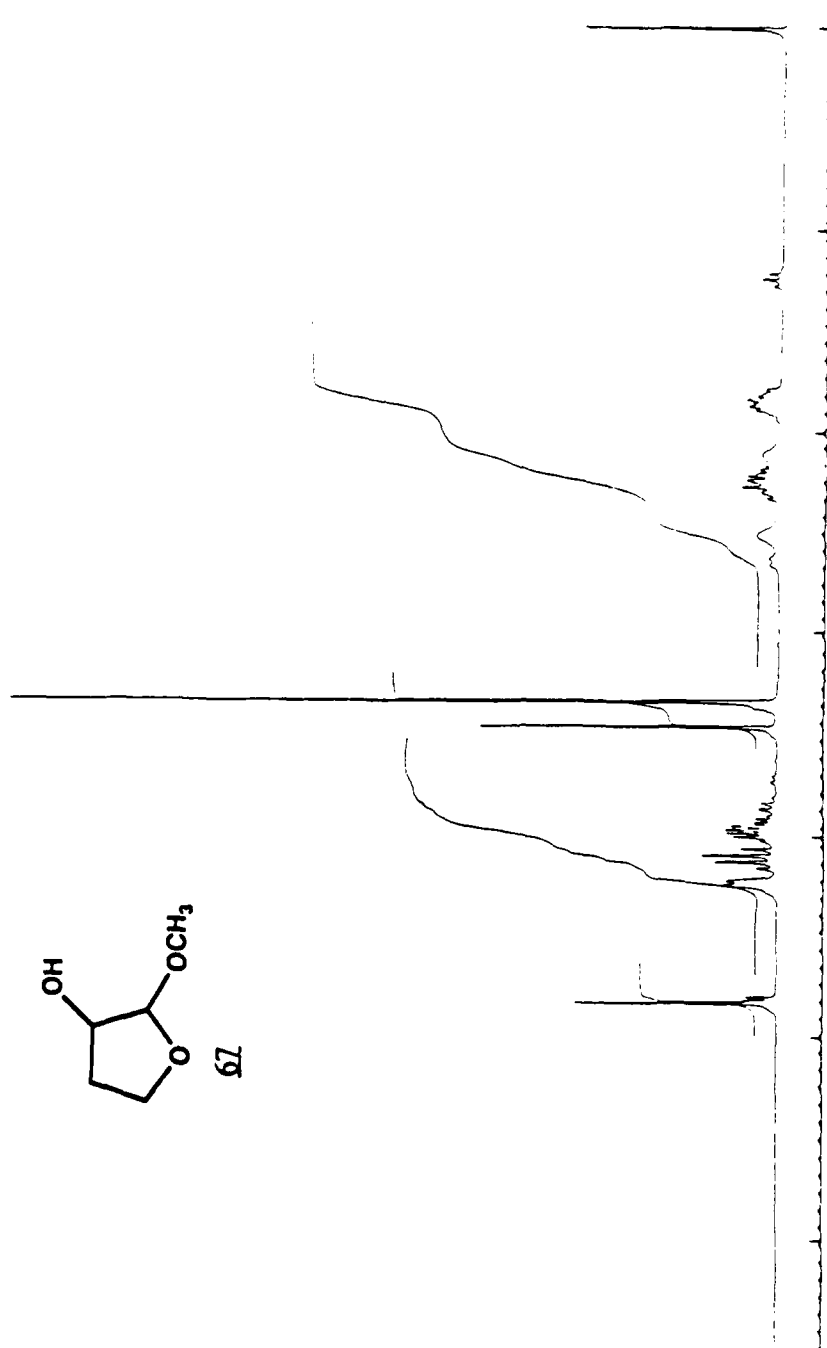


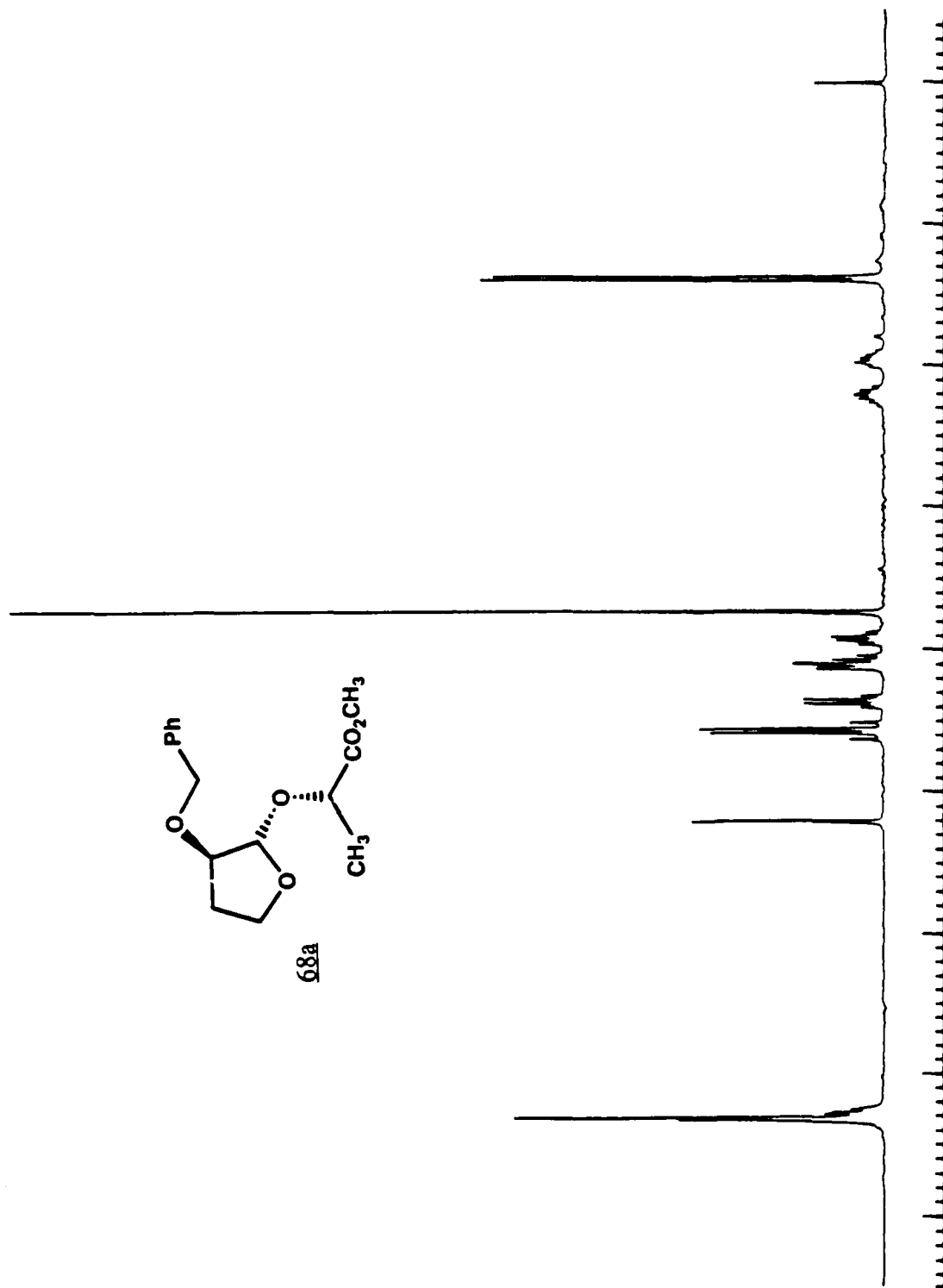


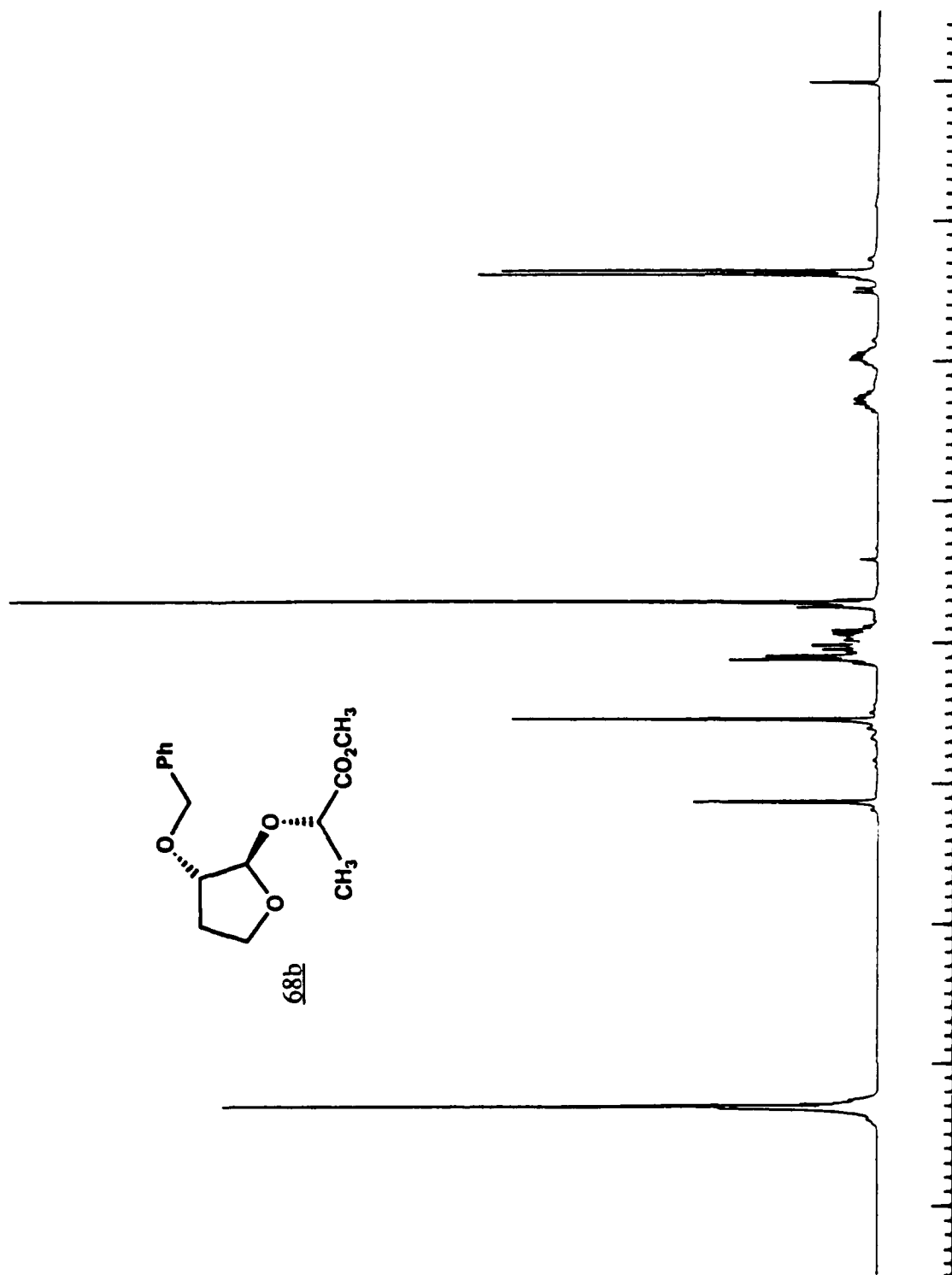


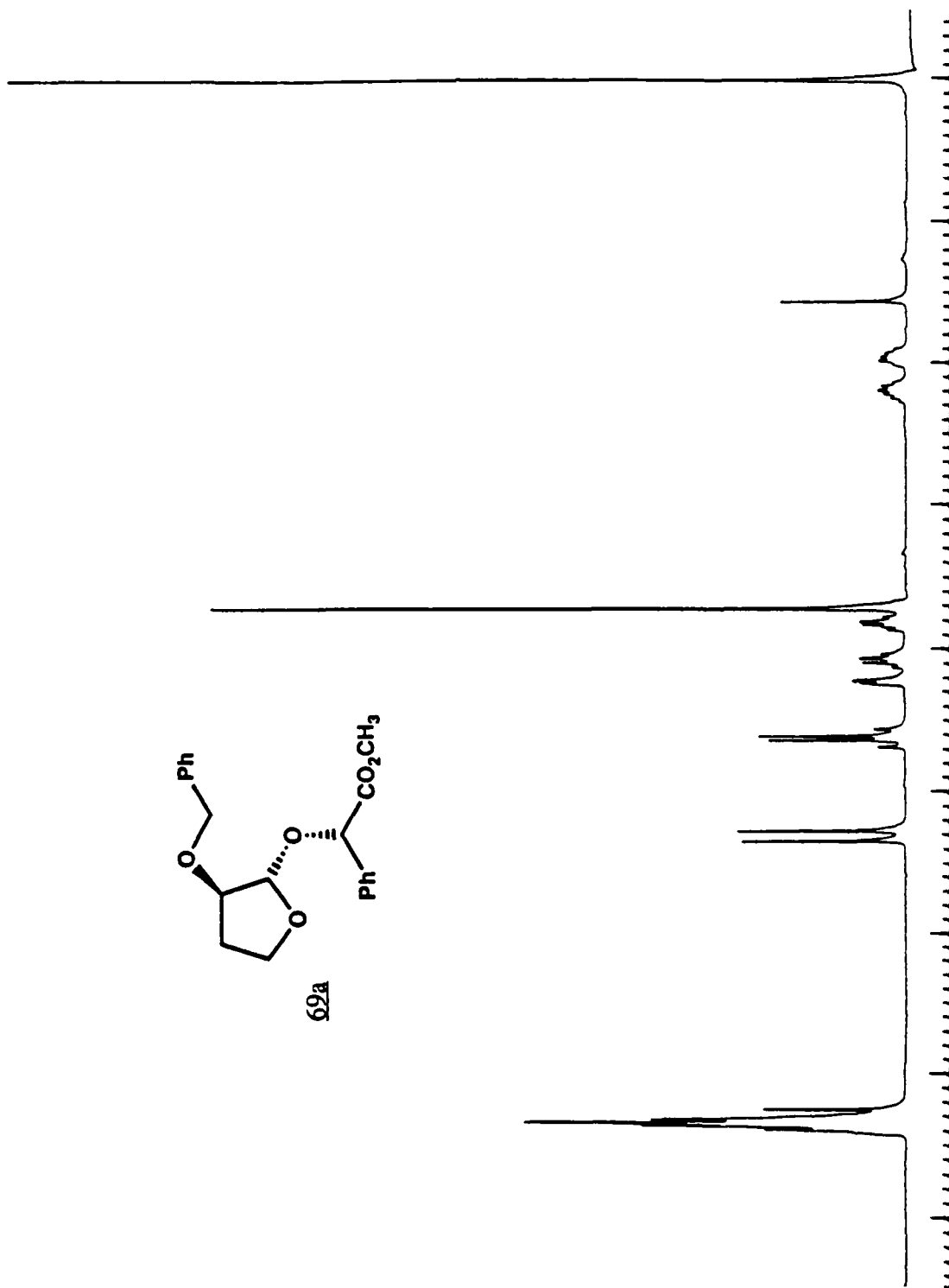
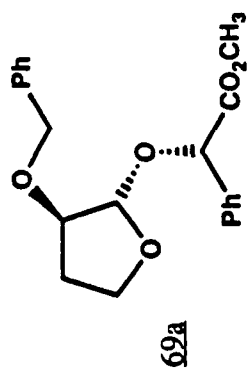


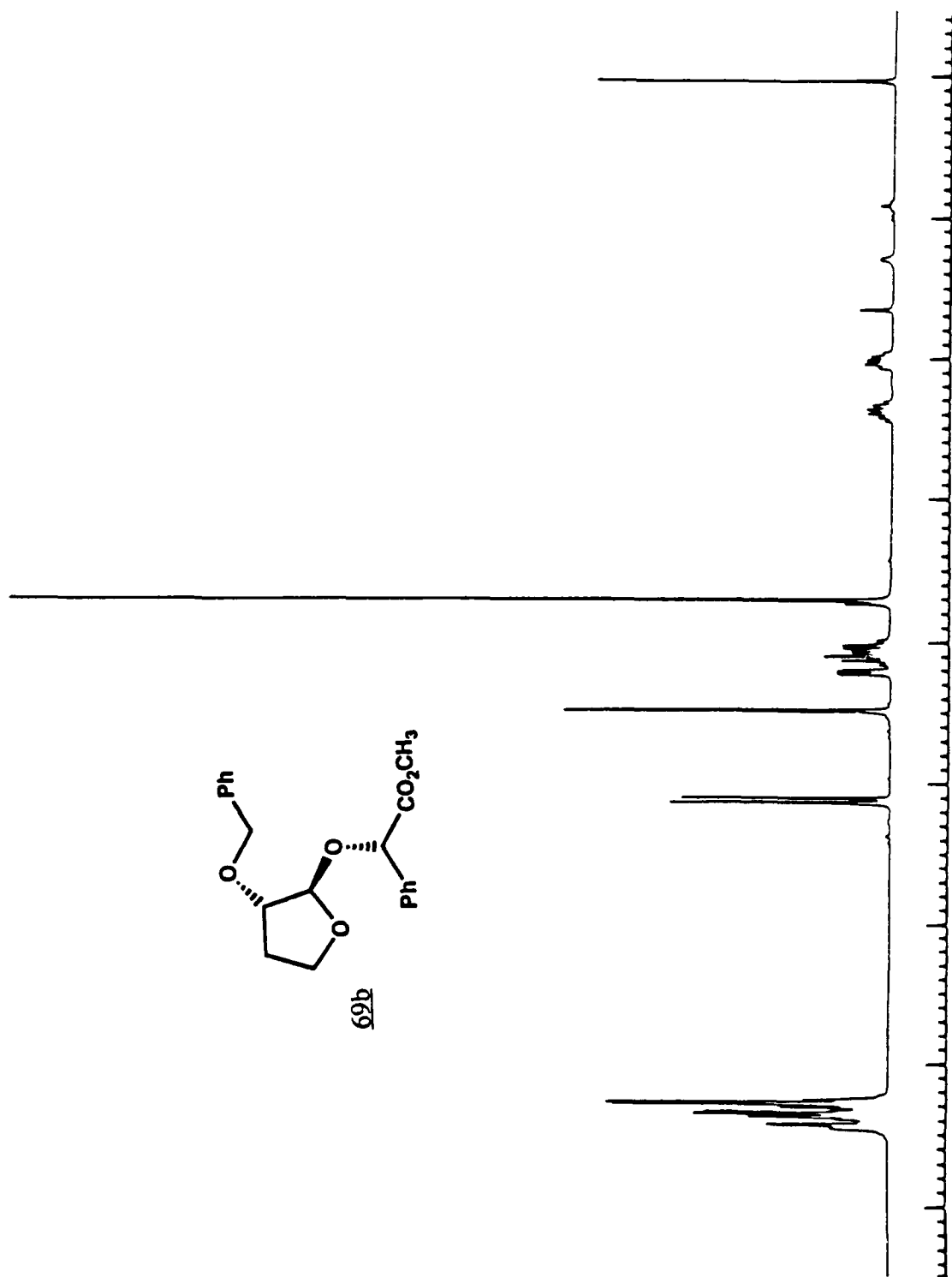


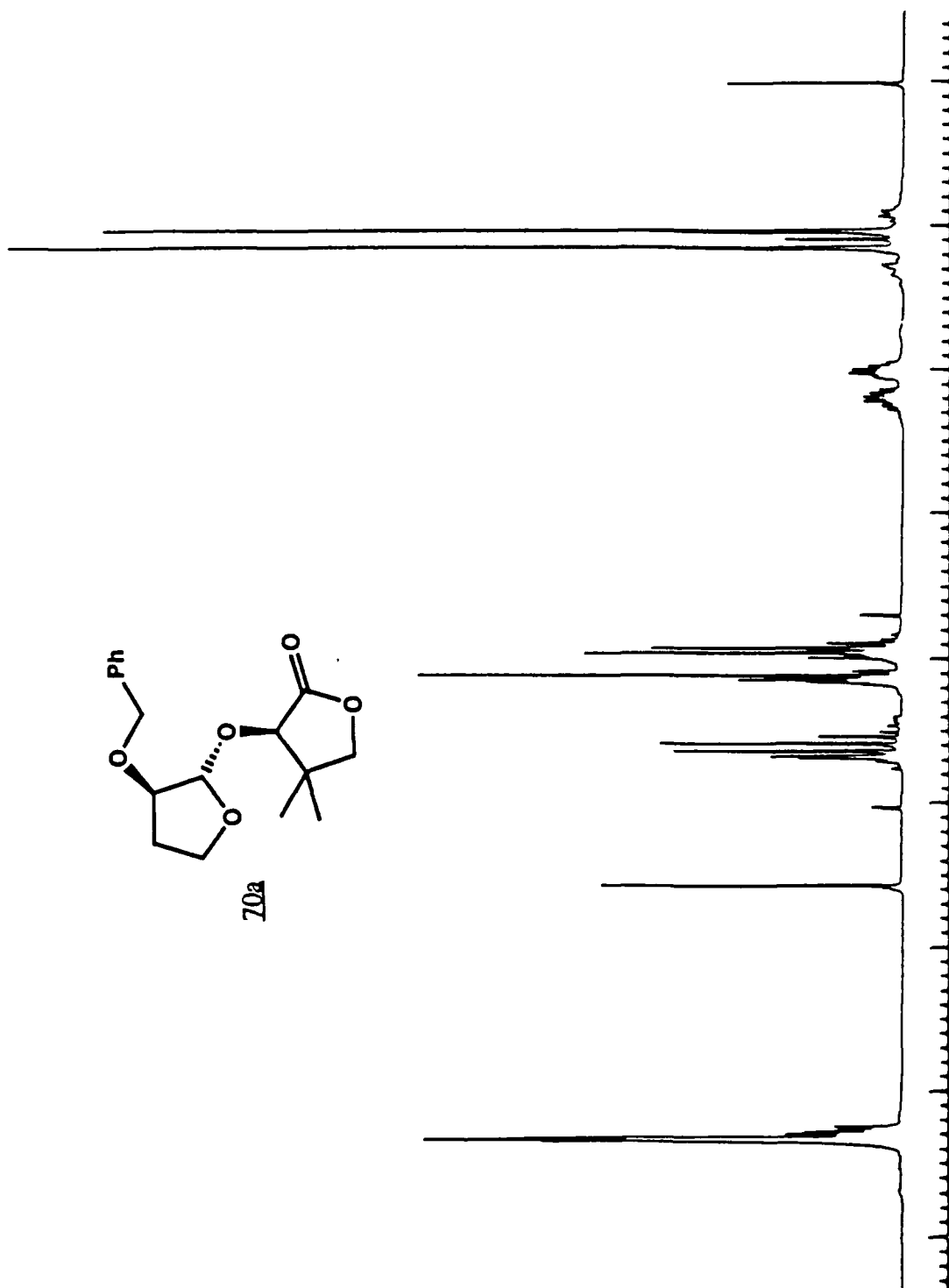


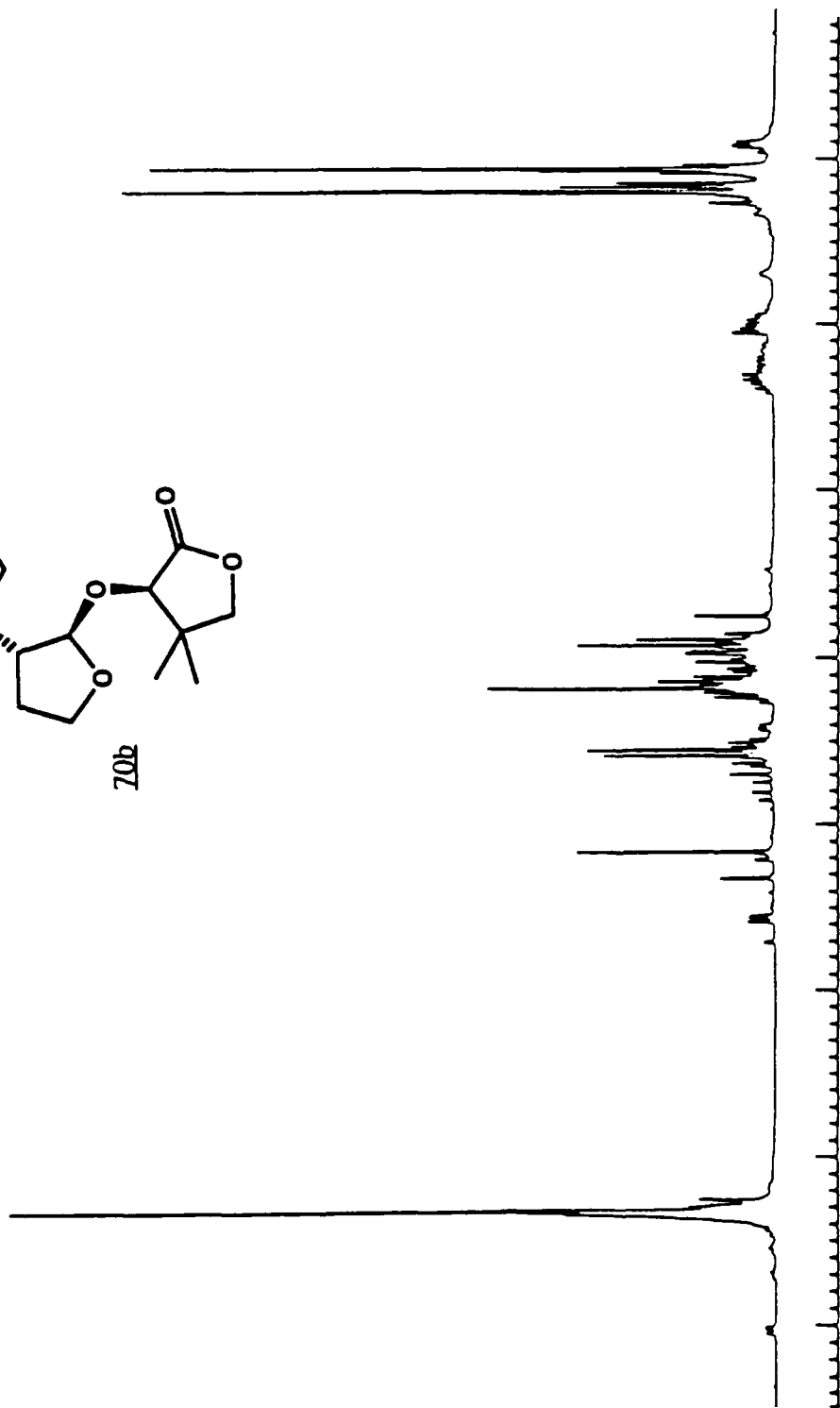
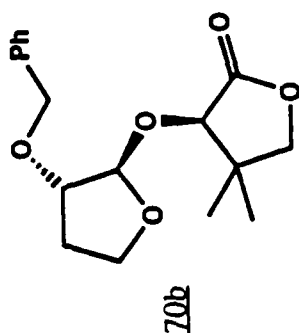


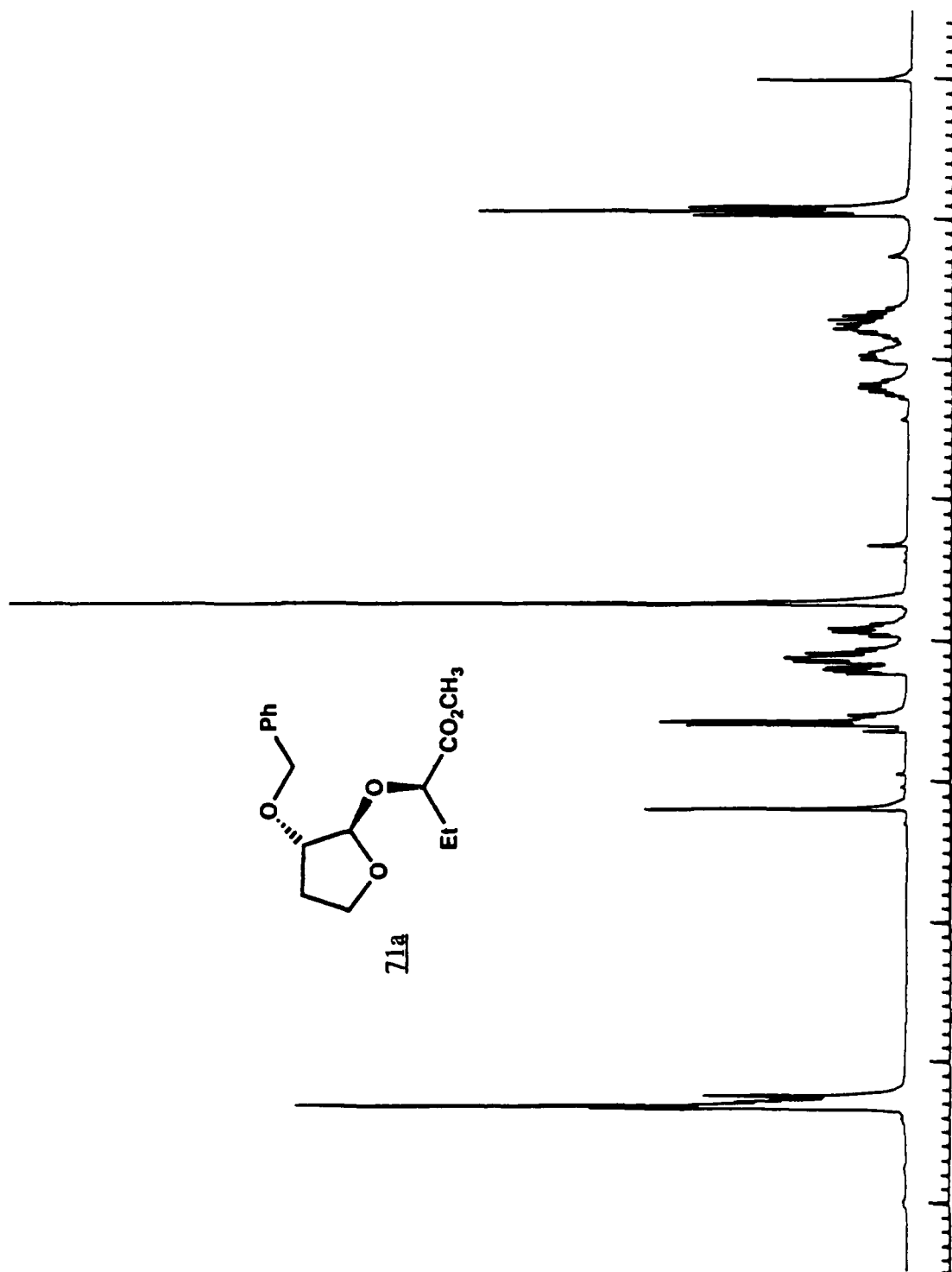


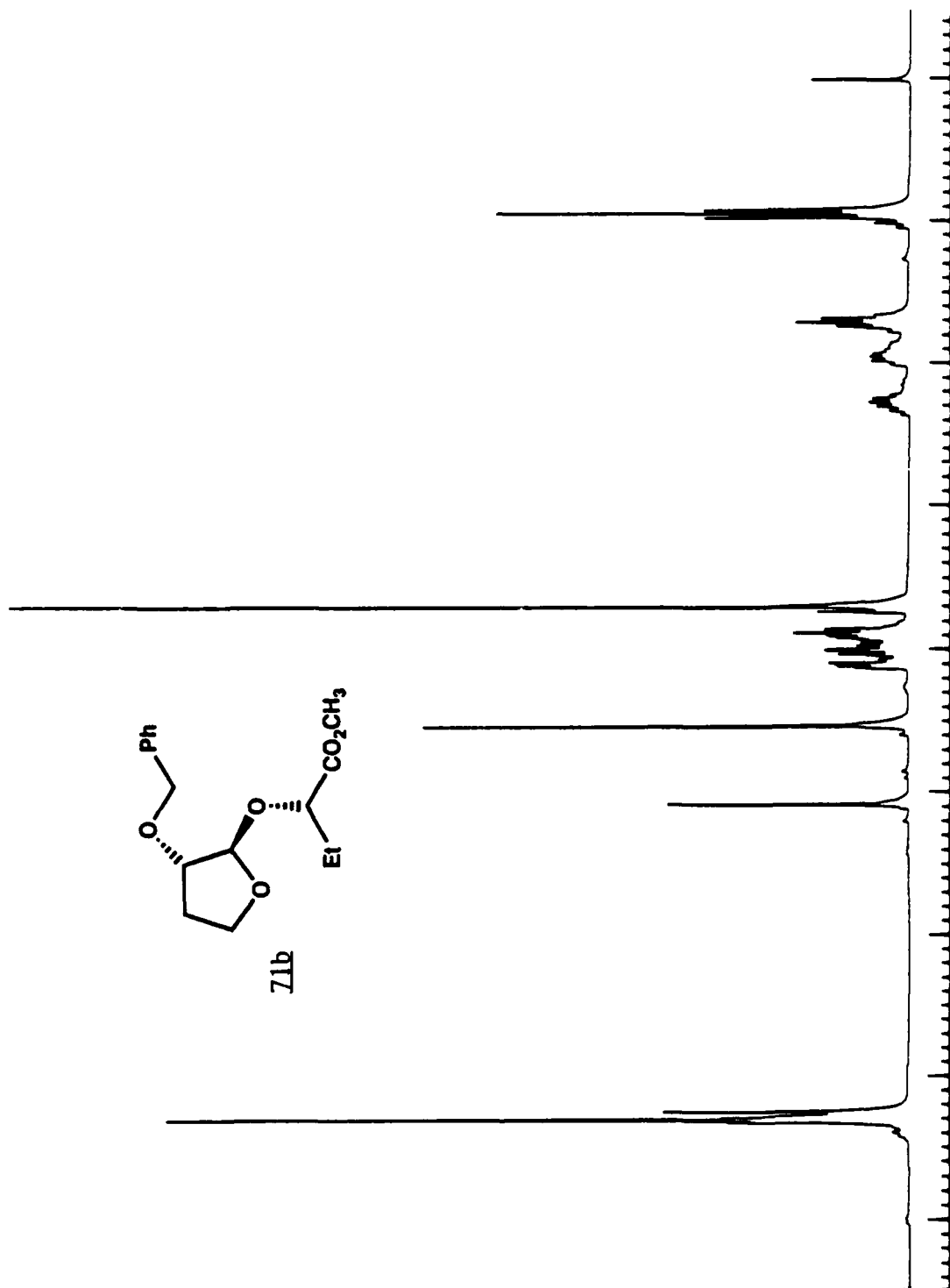


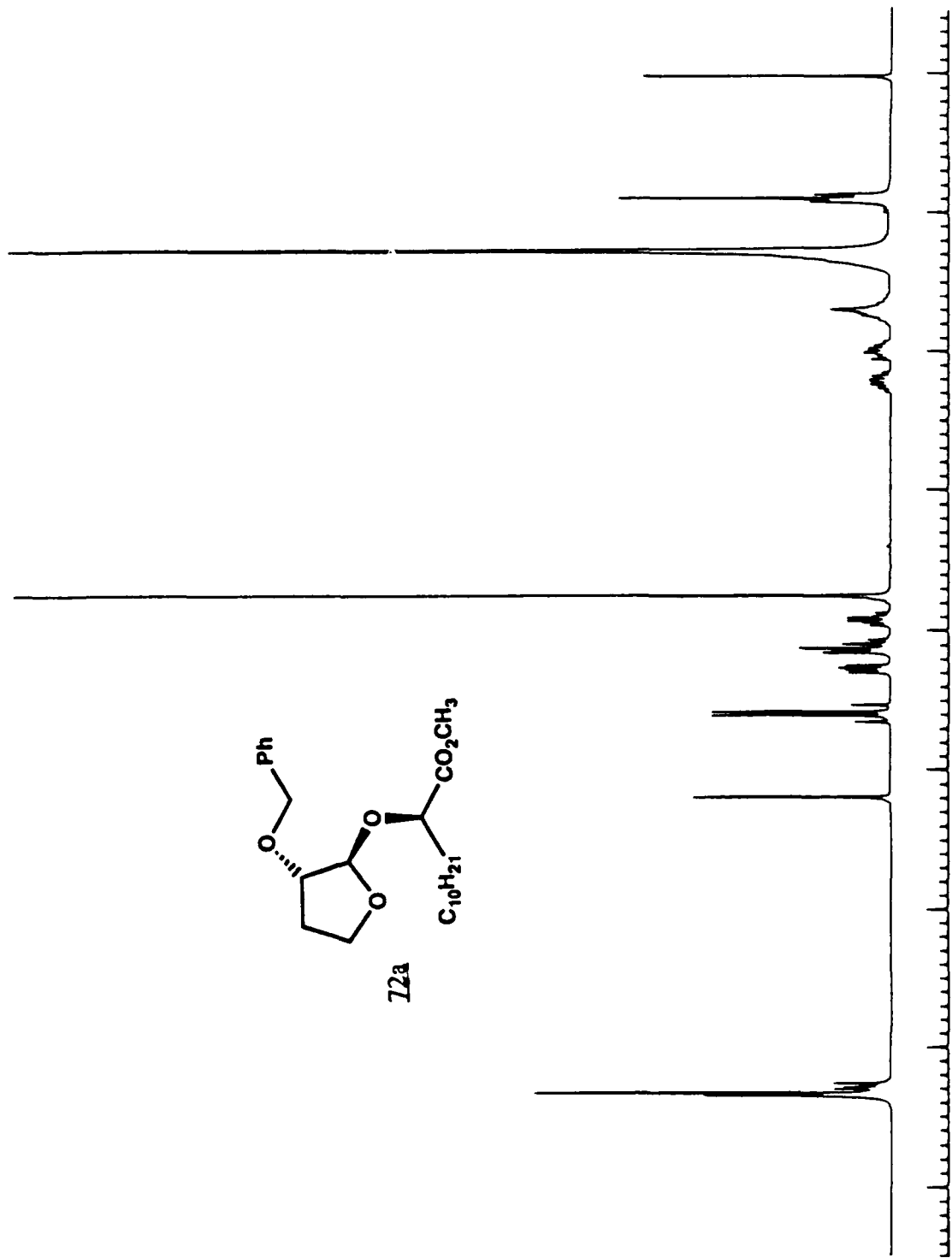
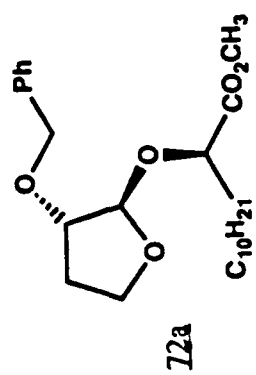


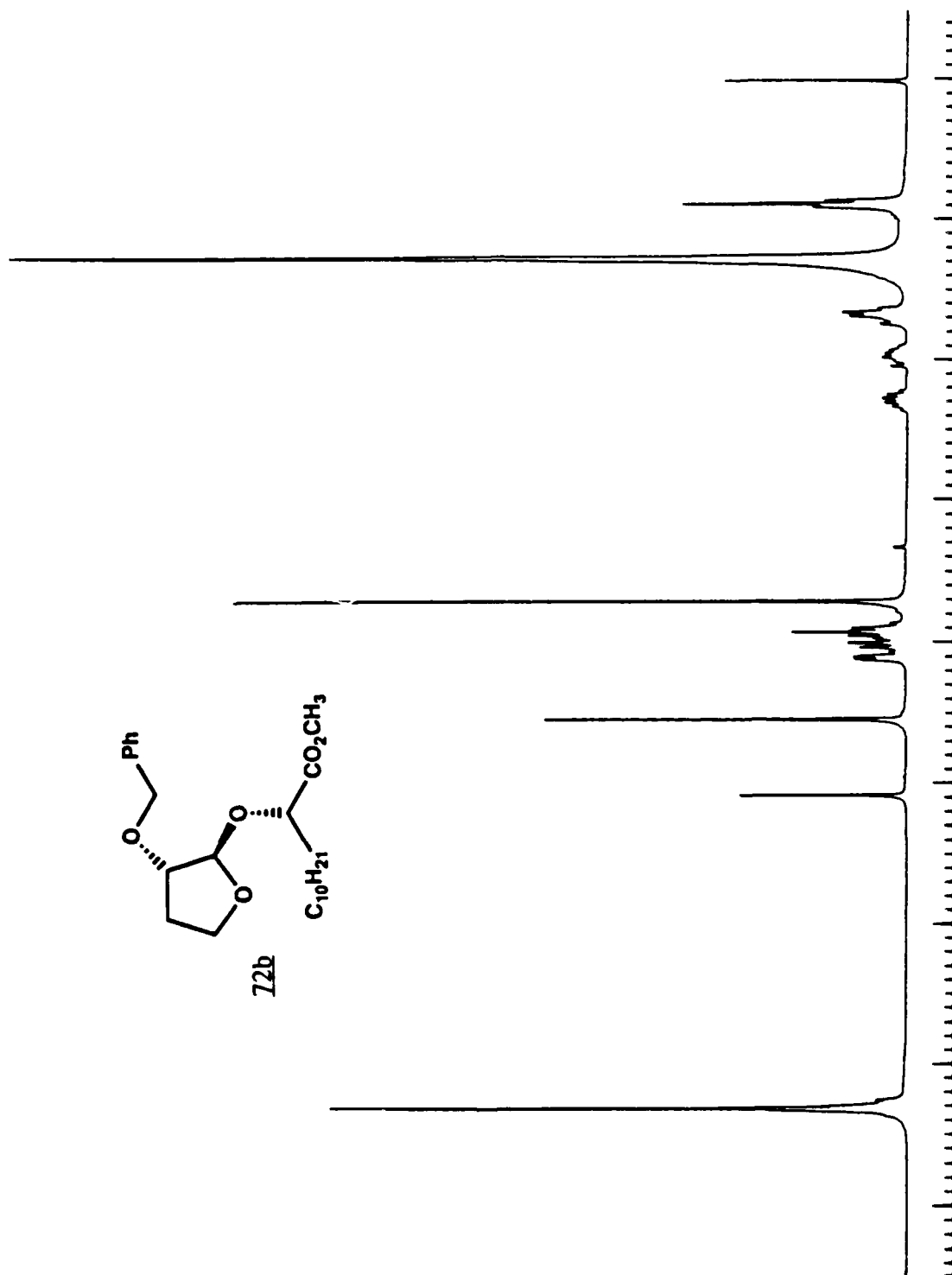


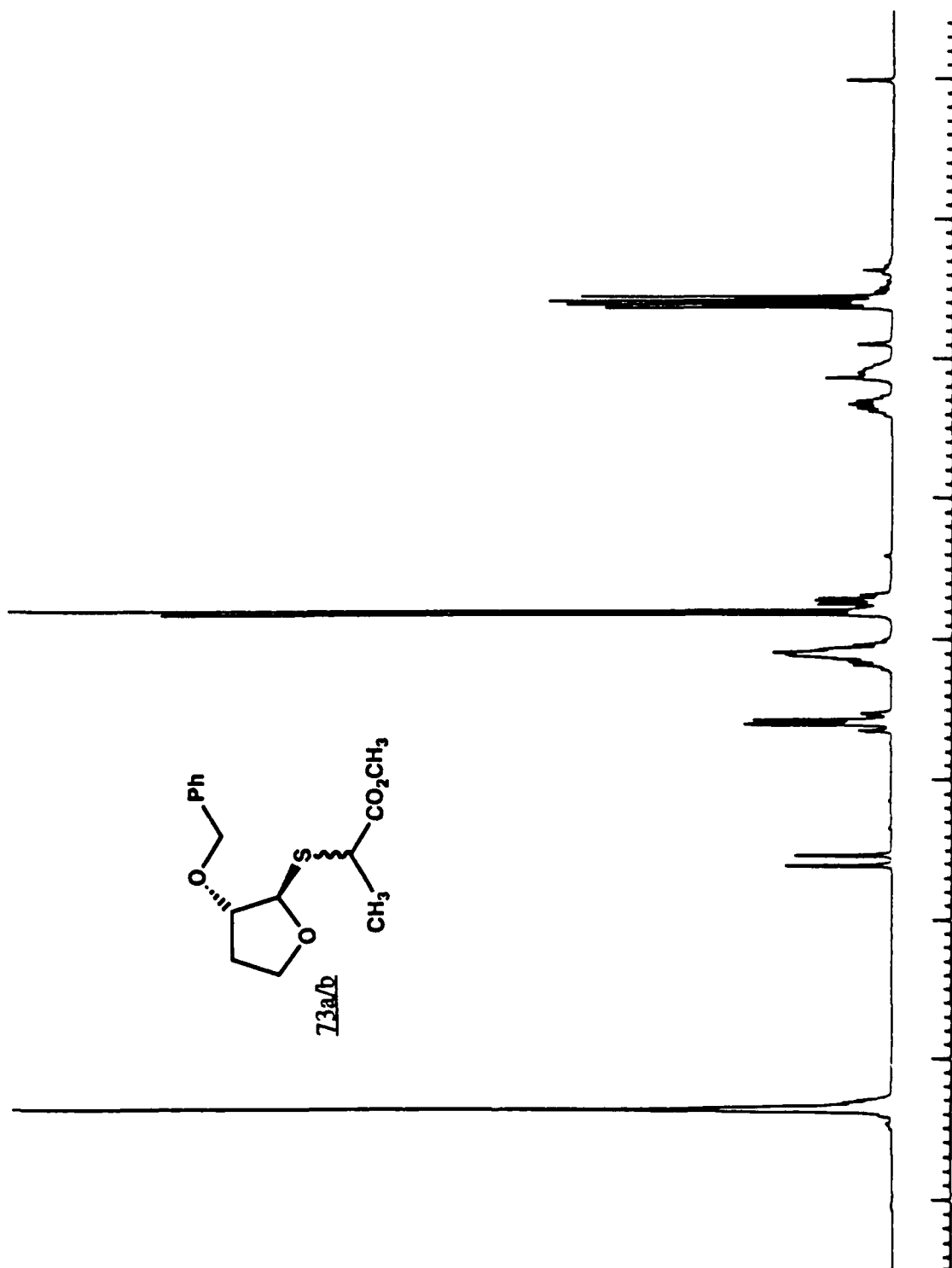


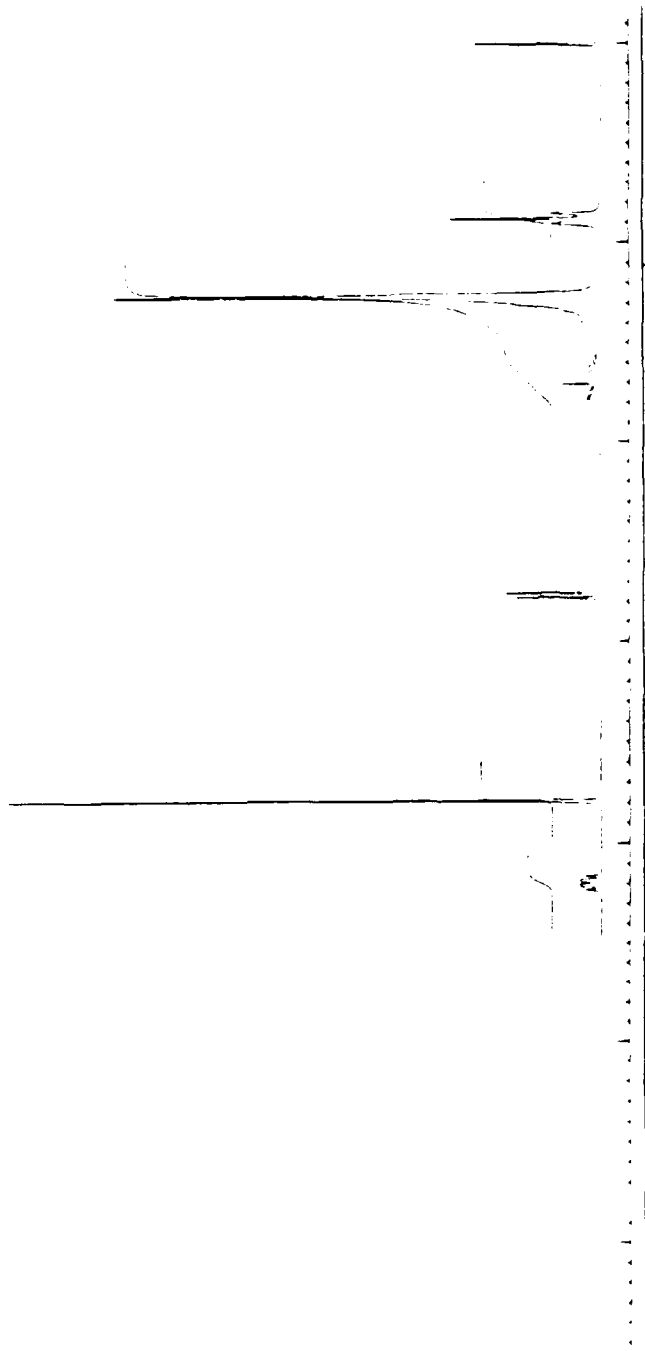
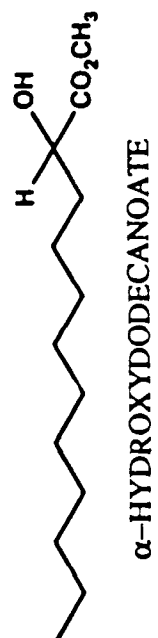




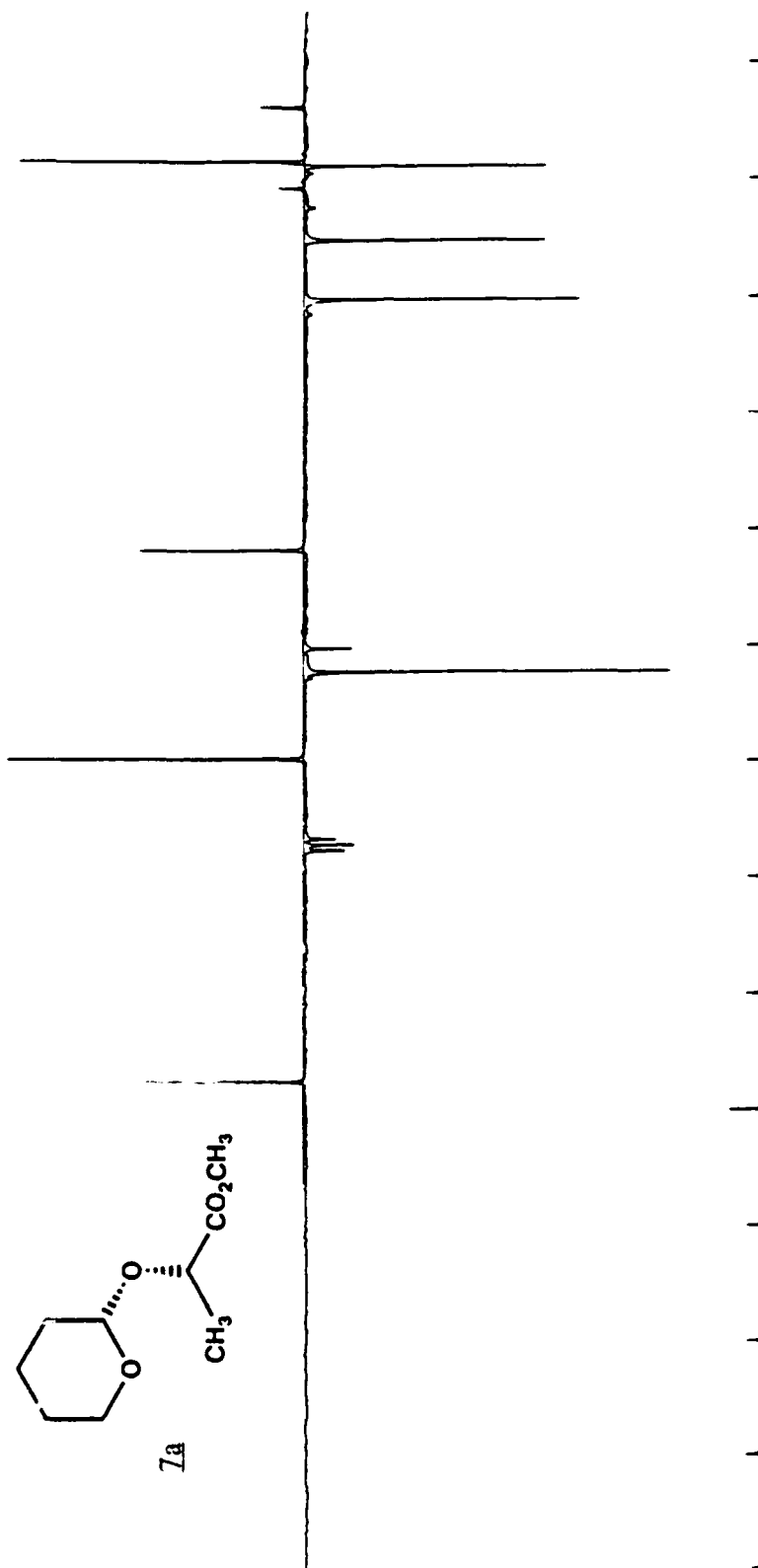


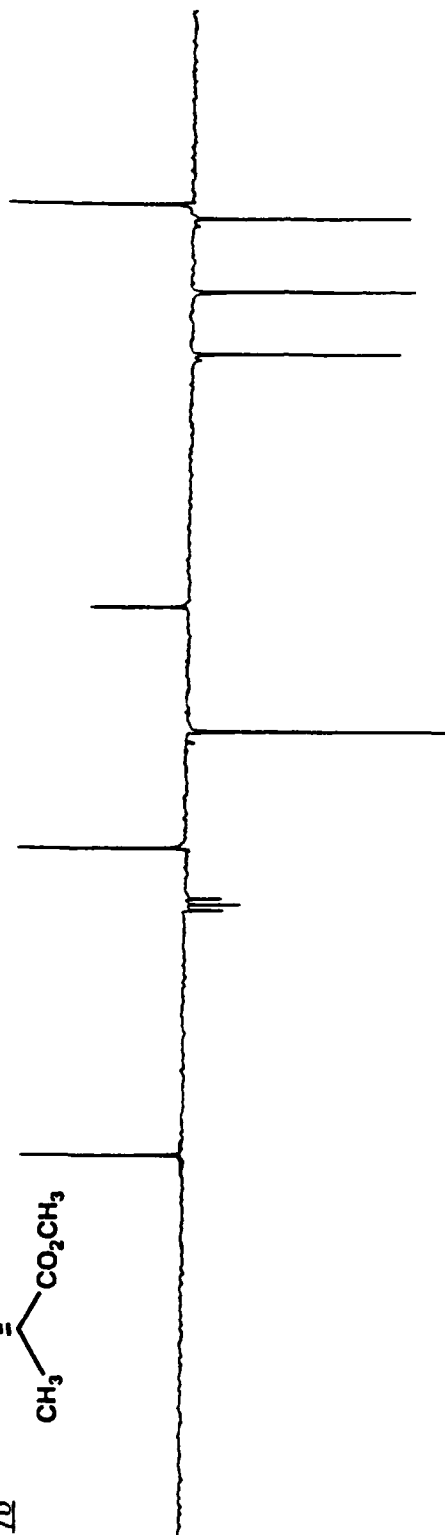
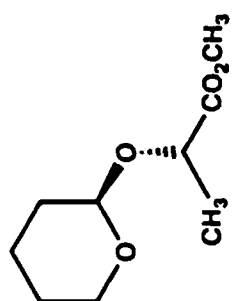


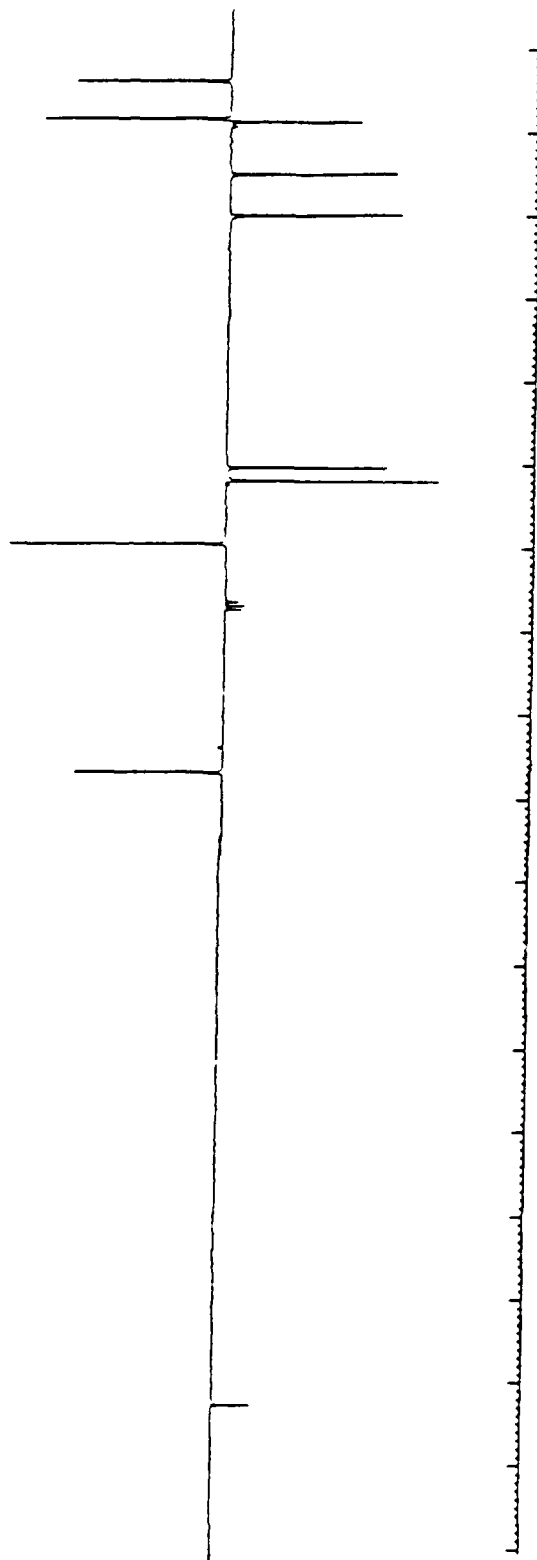
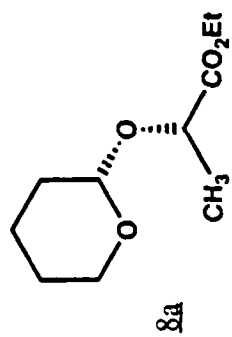


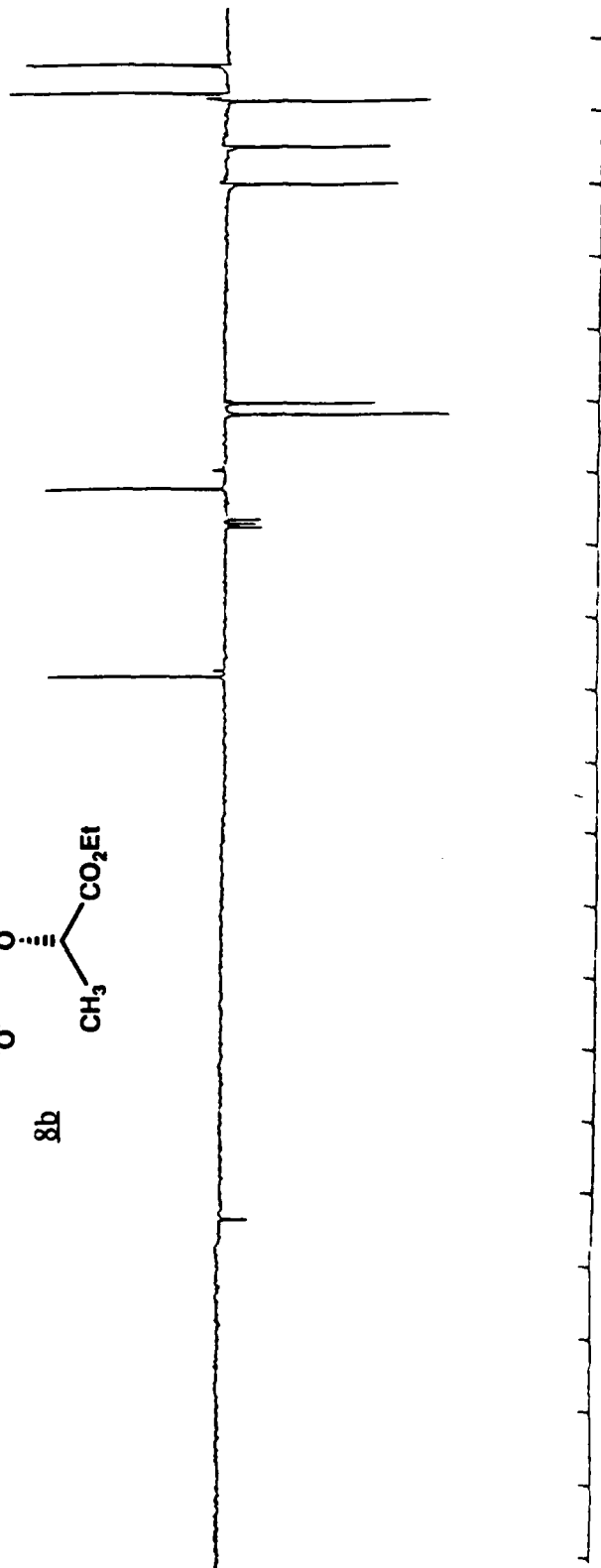
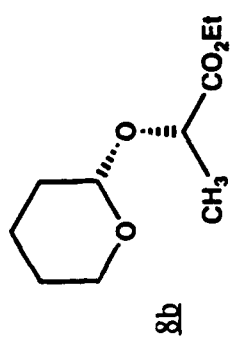


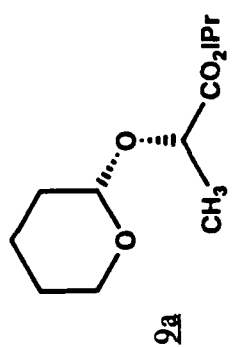
APPENDIX C: ^{13}C NMR OF SELECTED COMPOUNDS

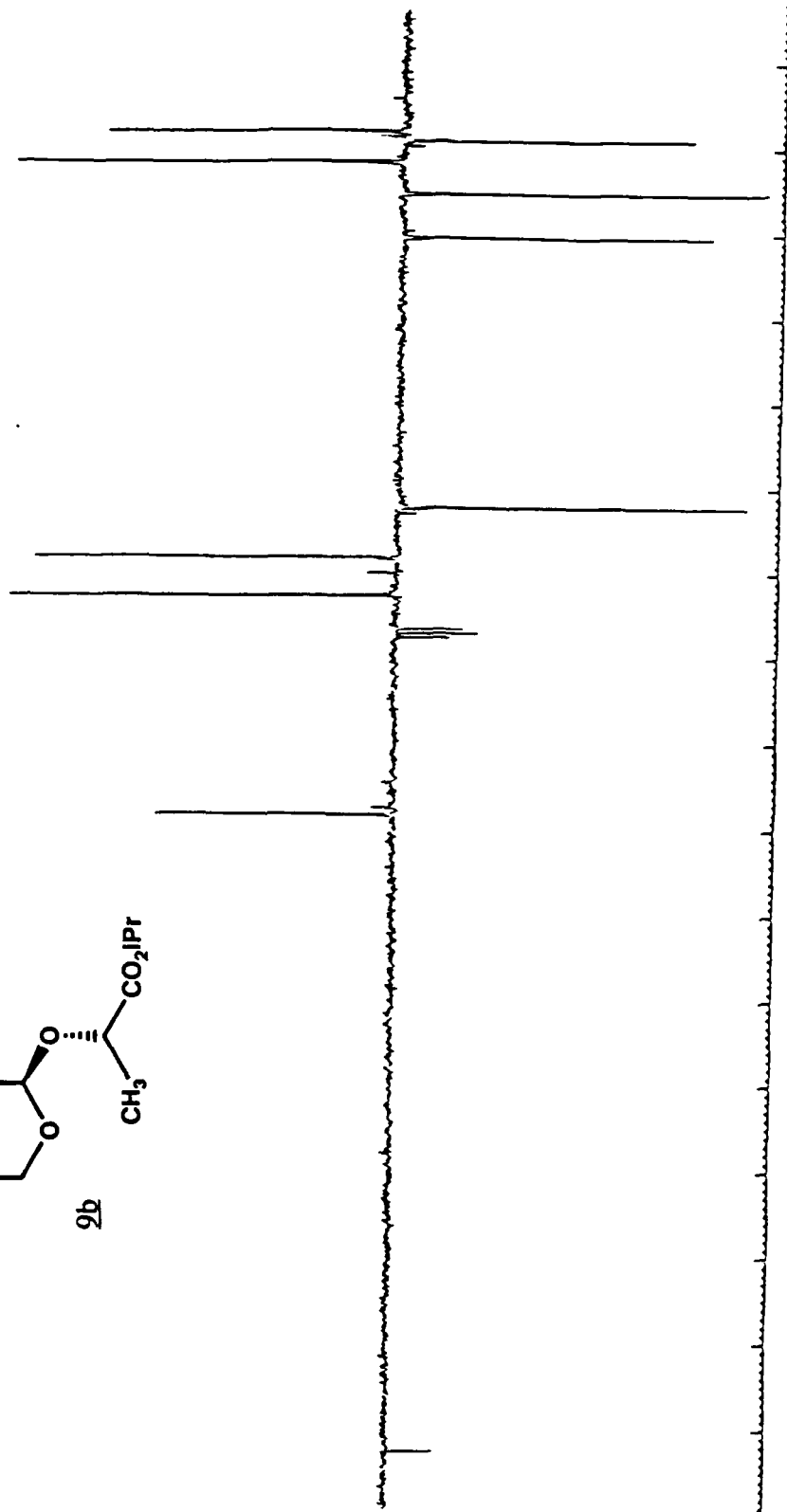
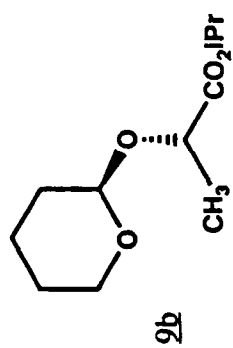


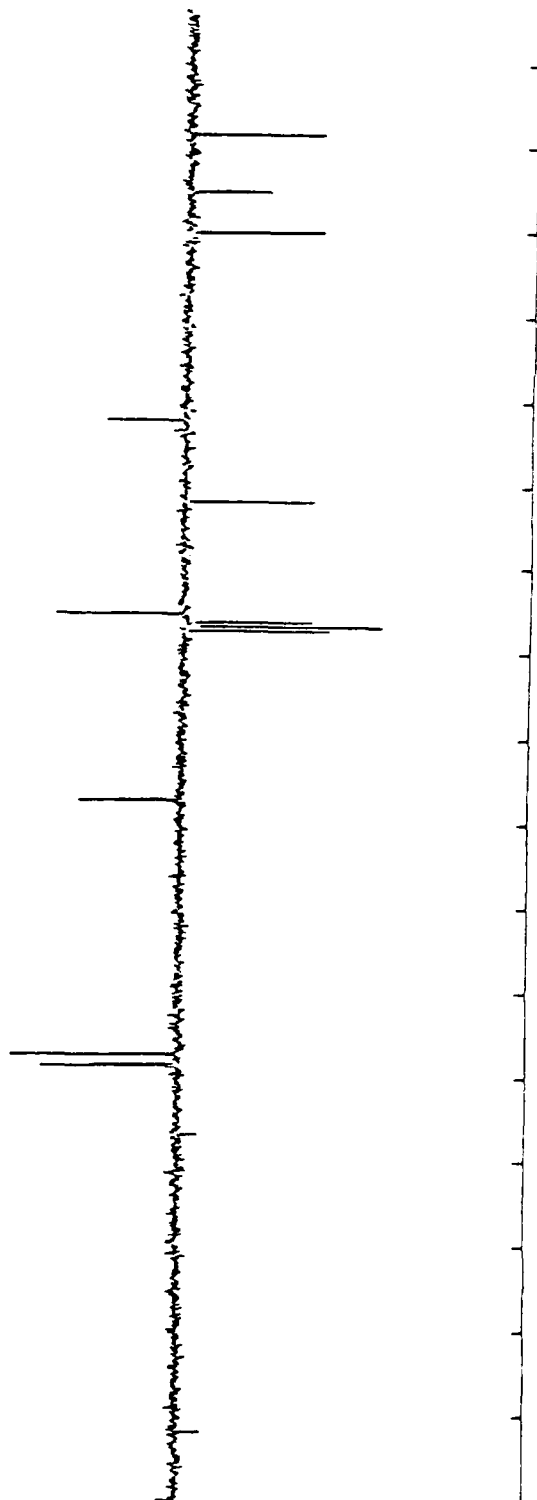
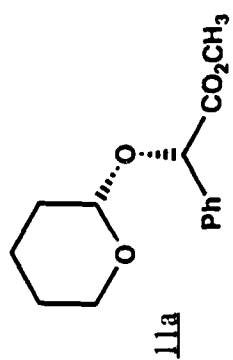


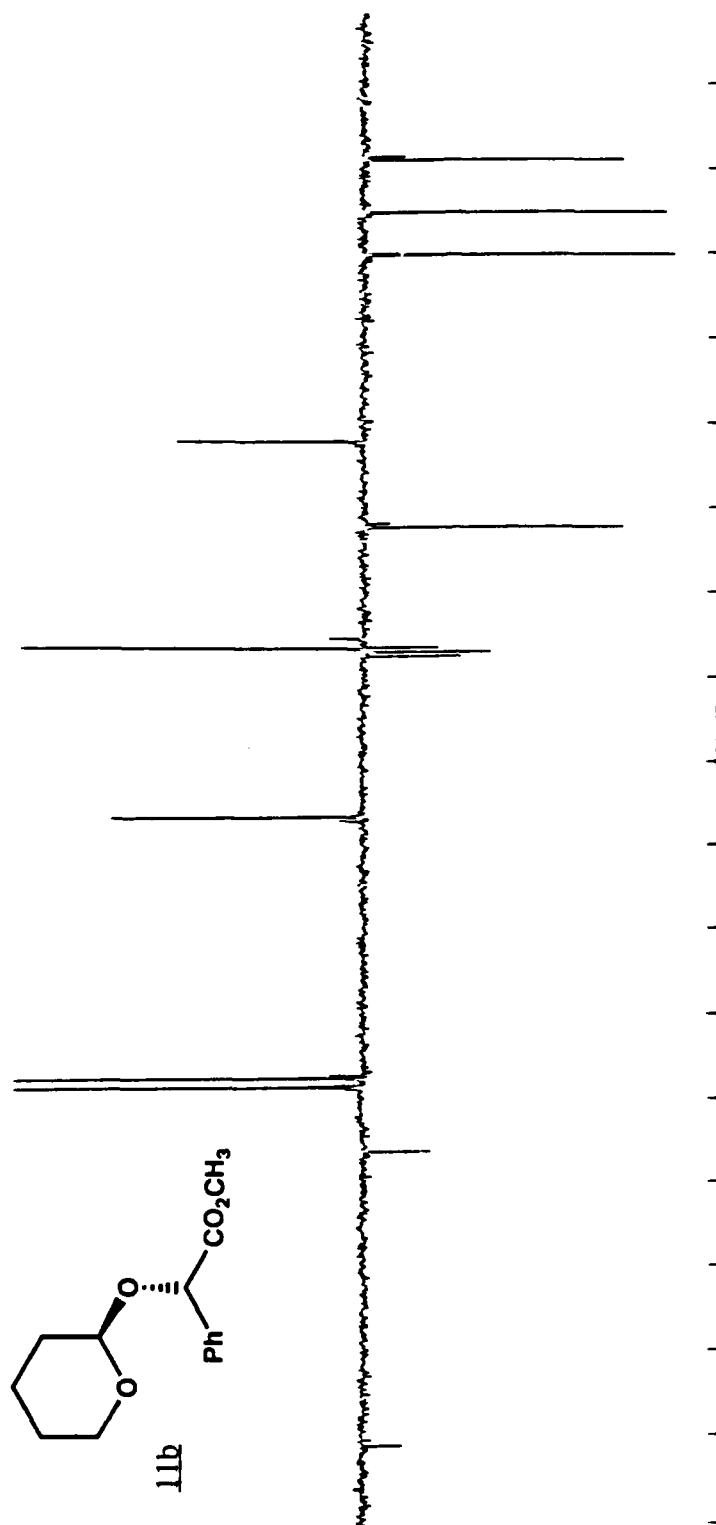


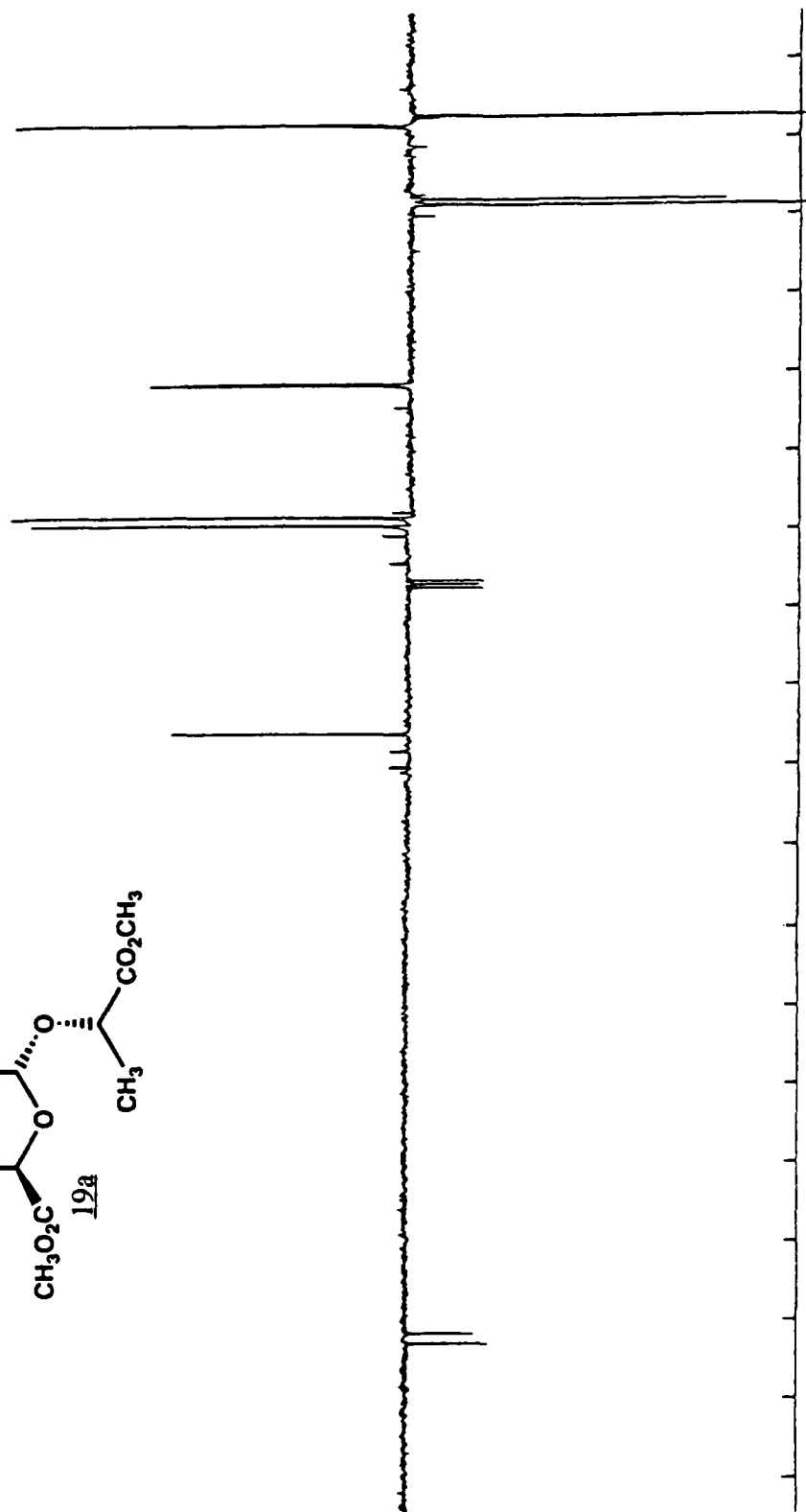
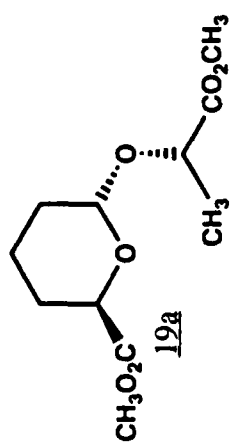


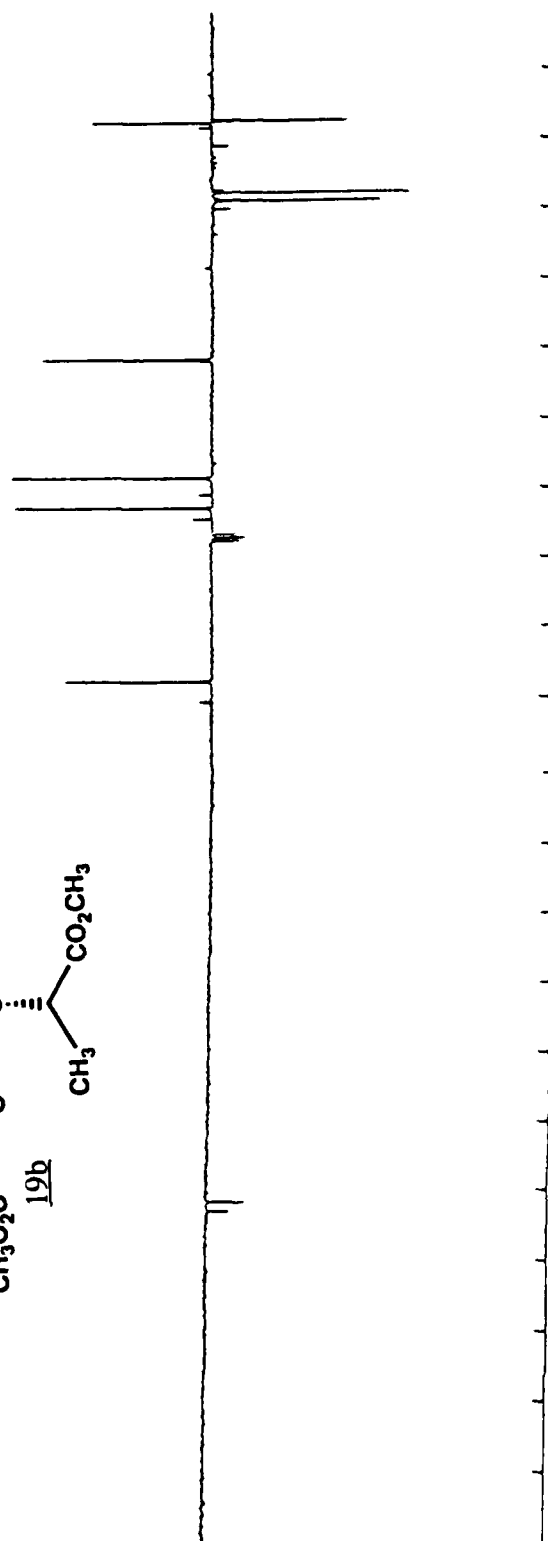
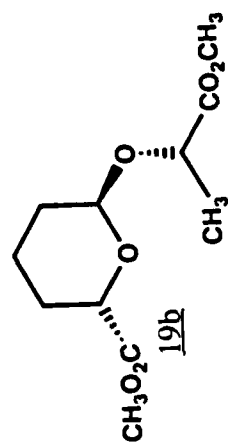


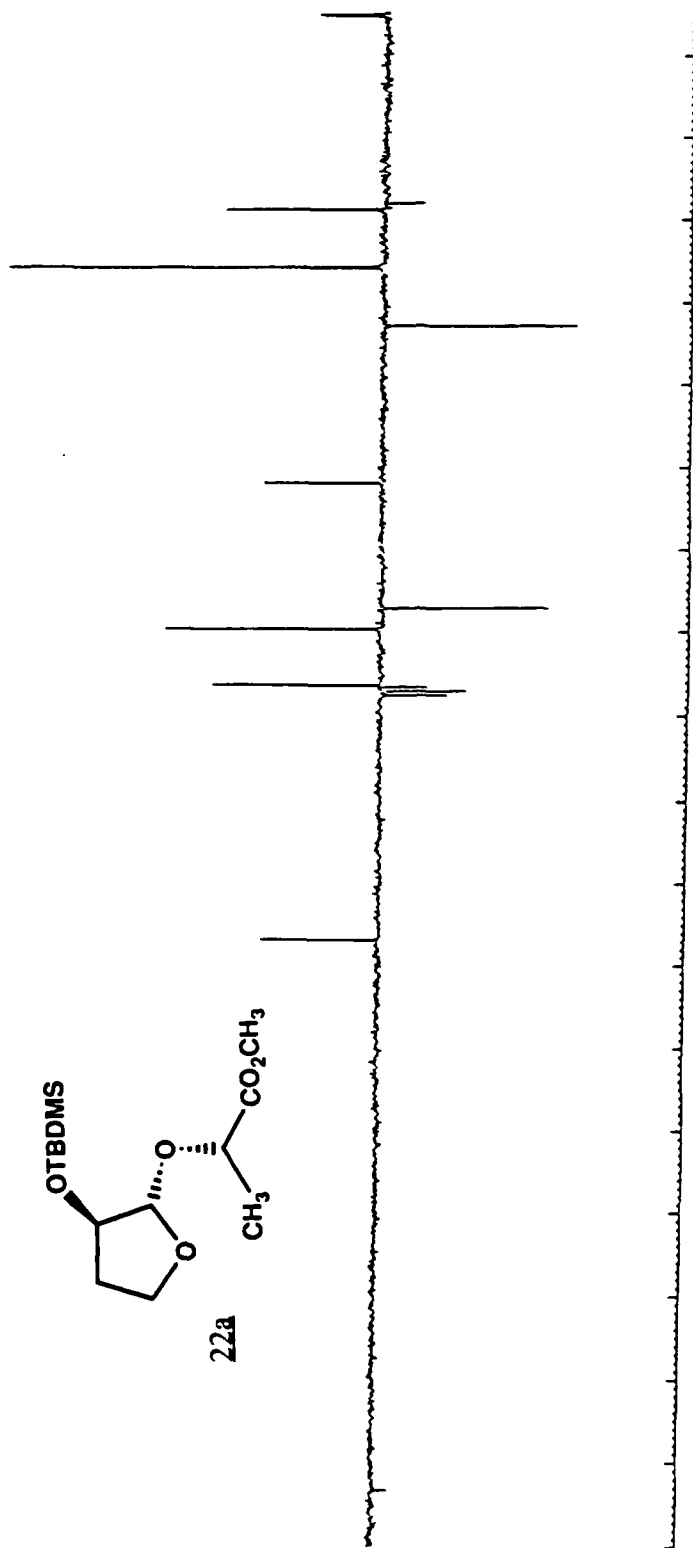


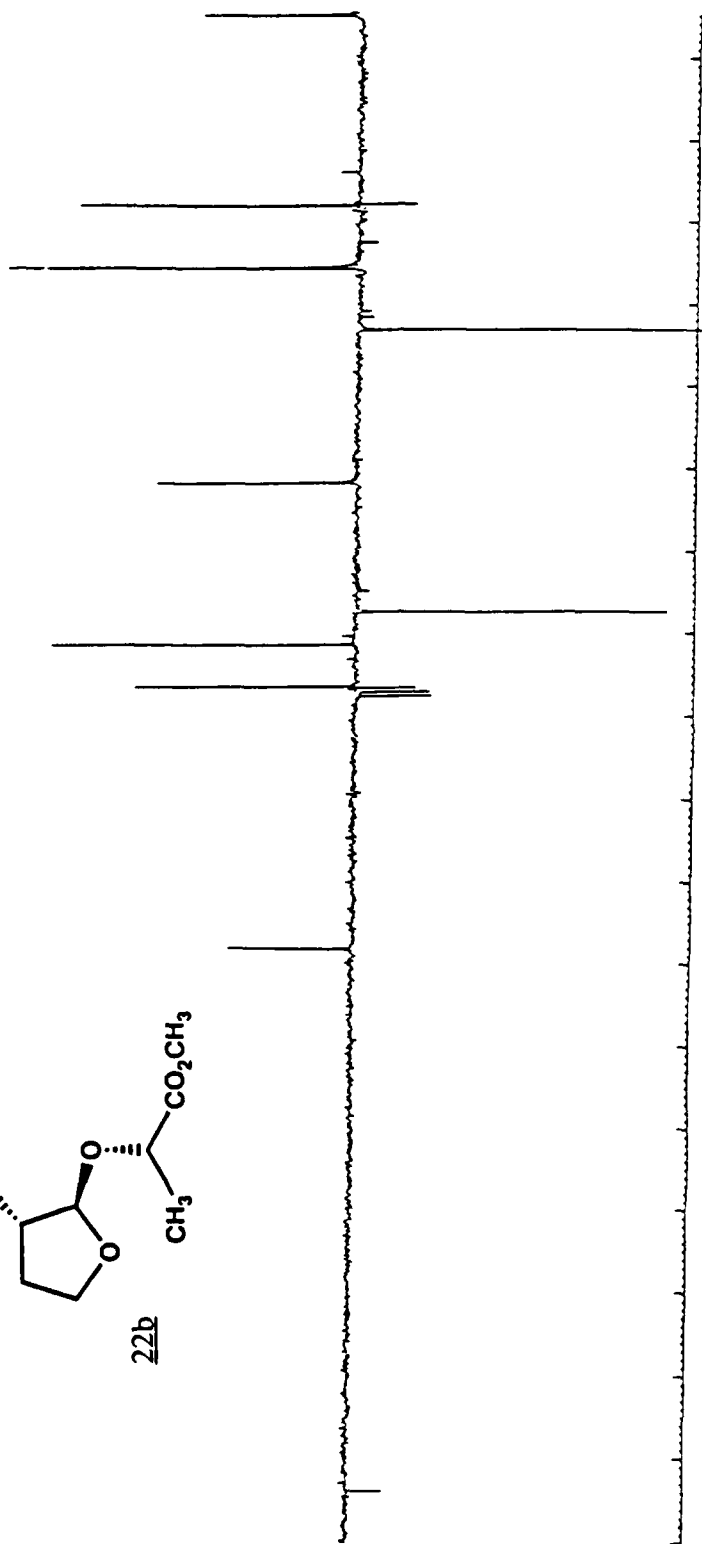
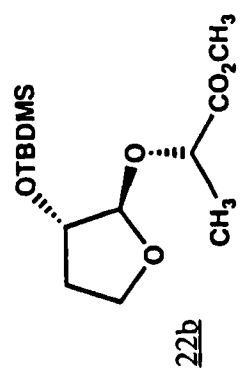


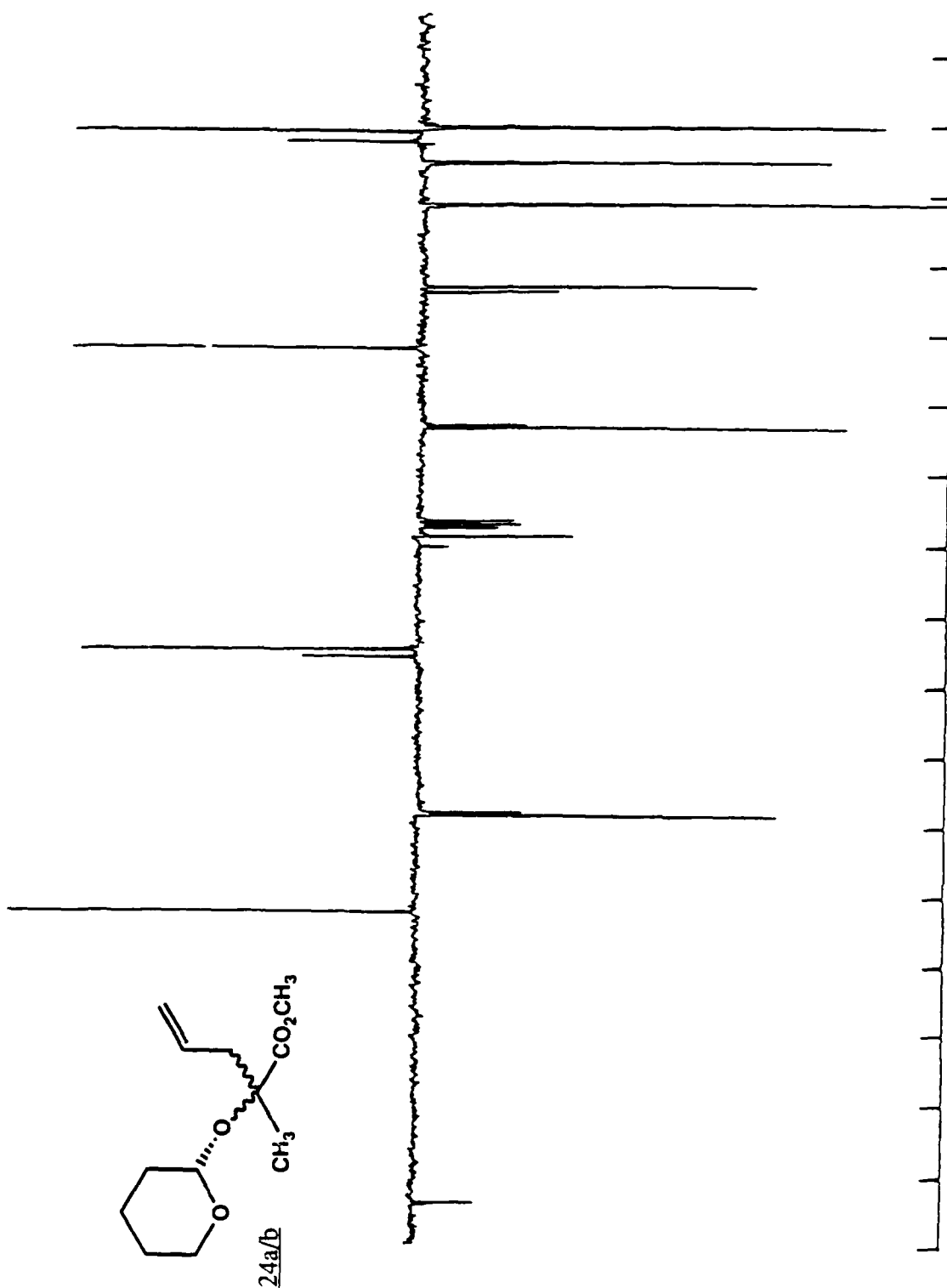


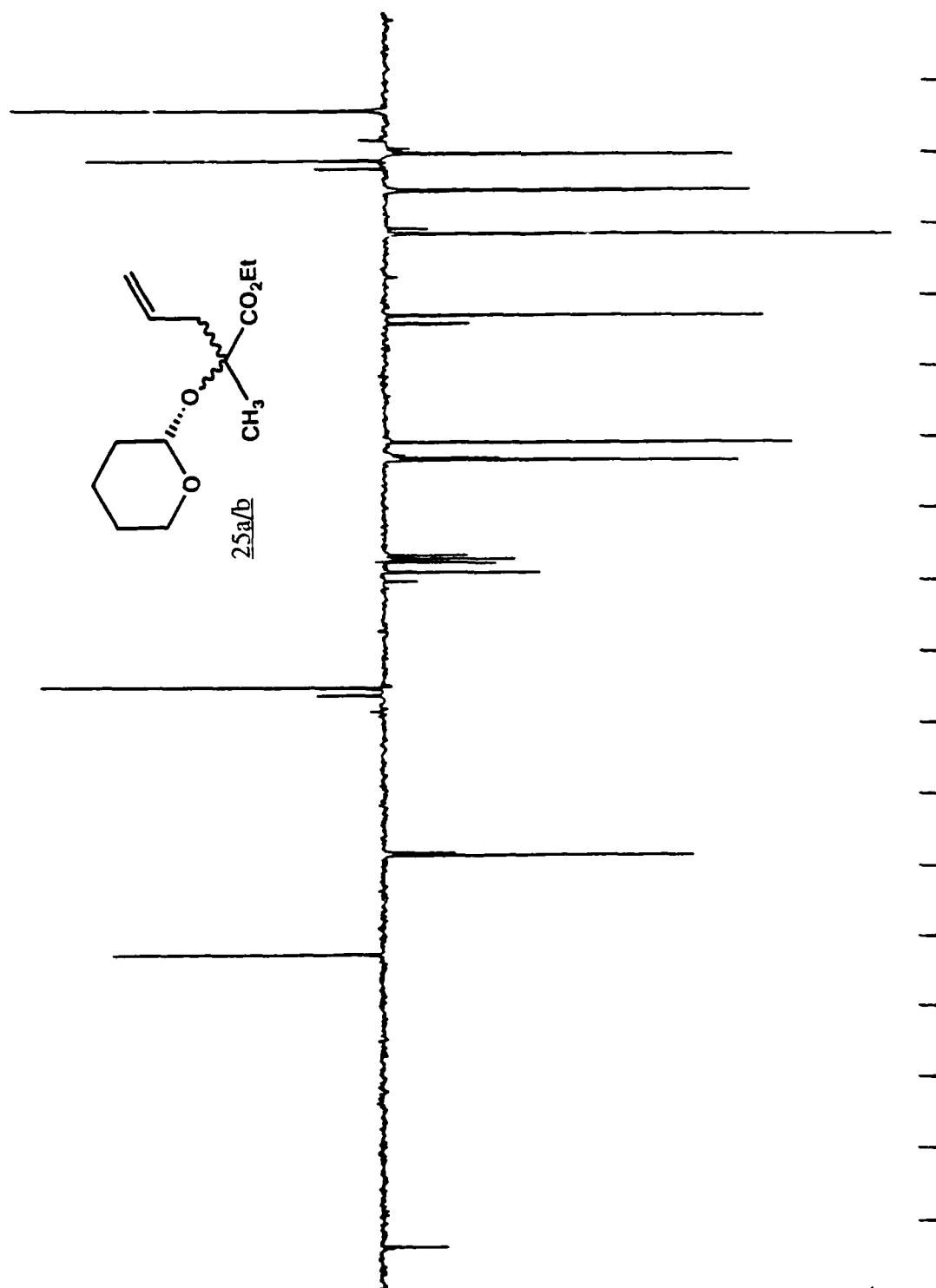


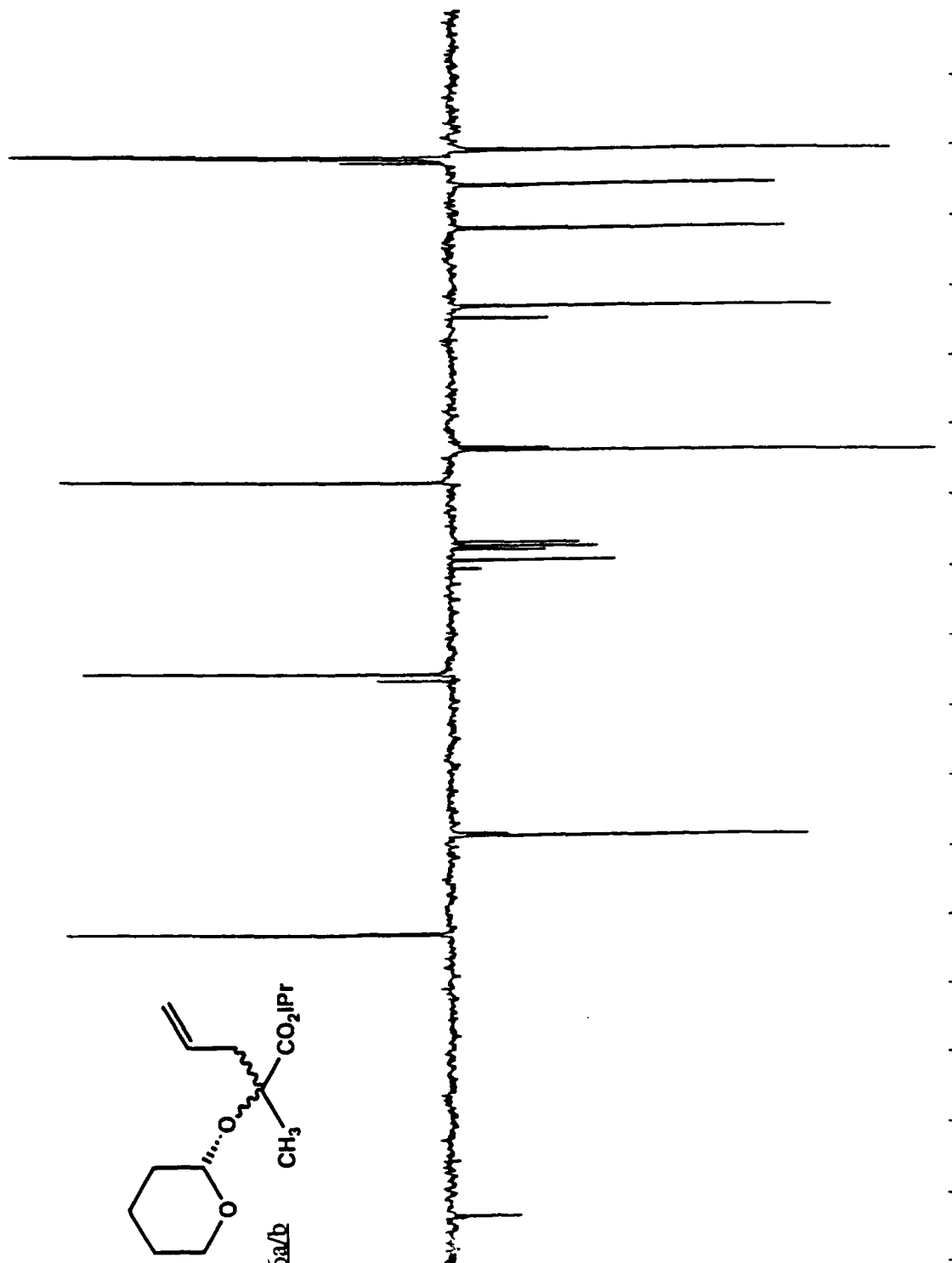
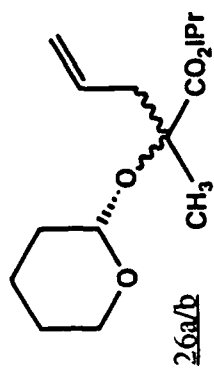


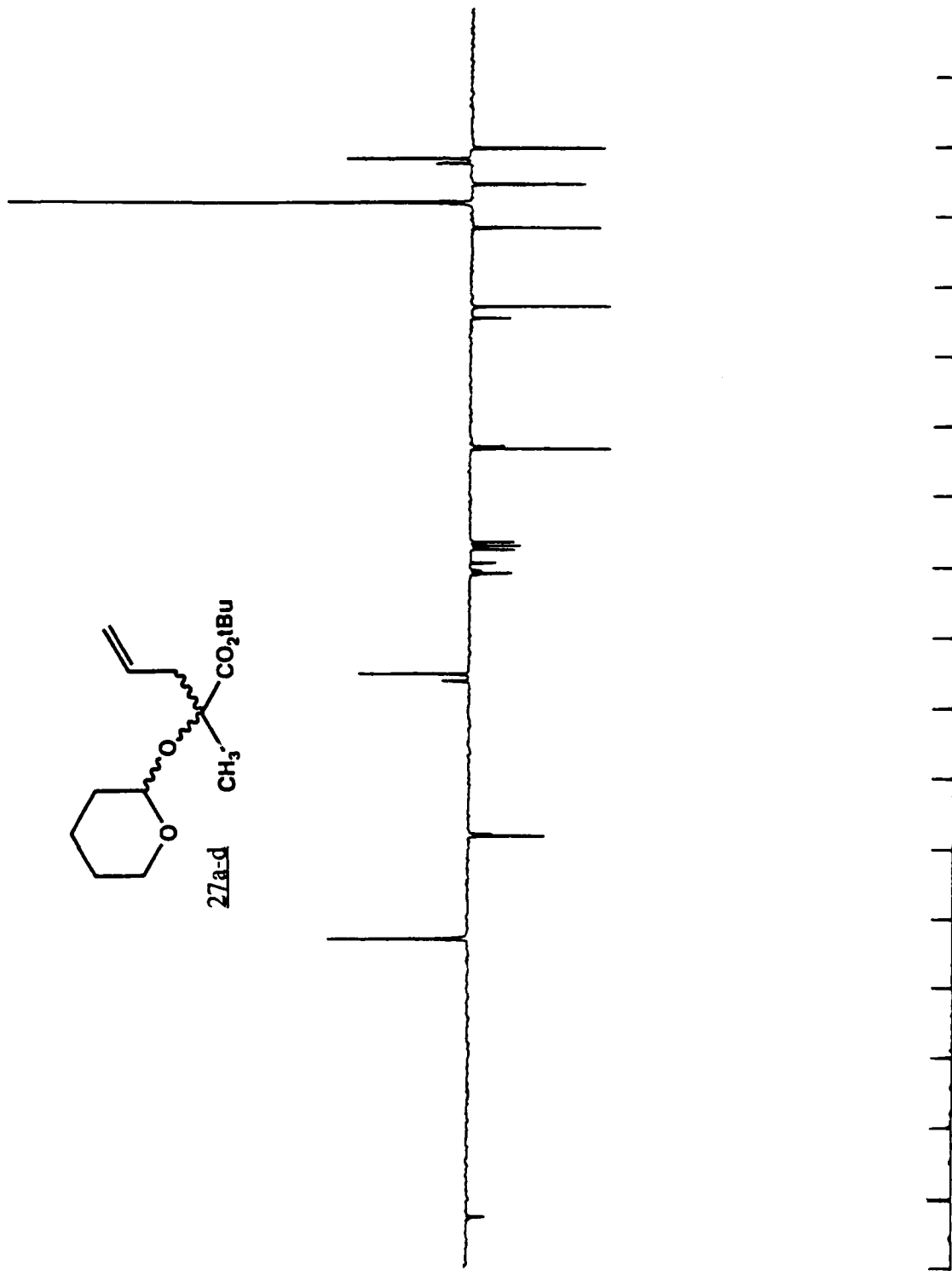
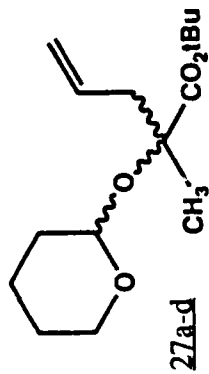


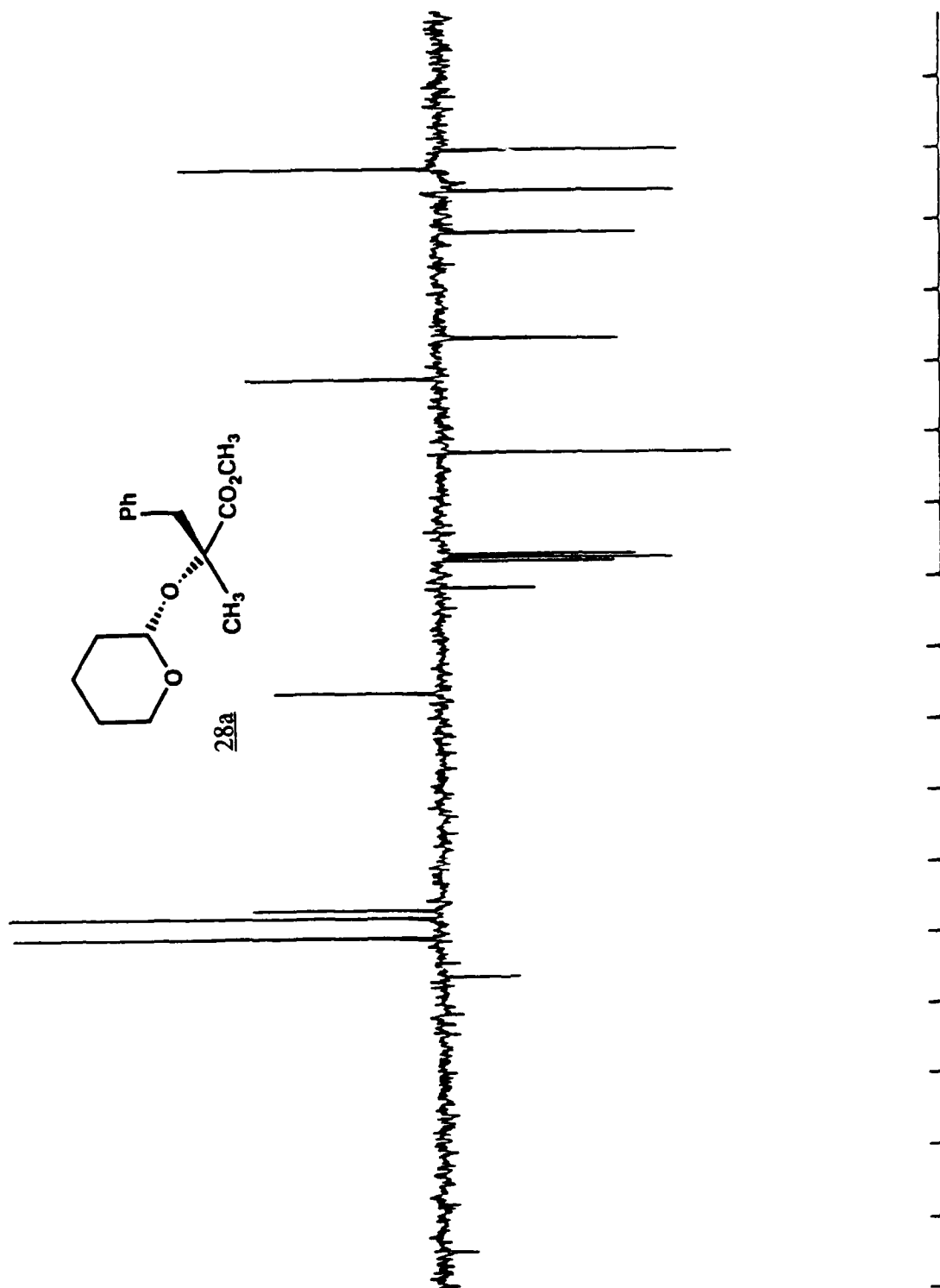


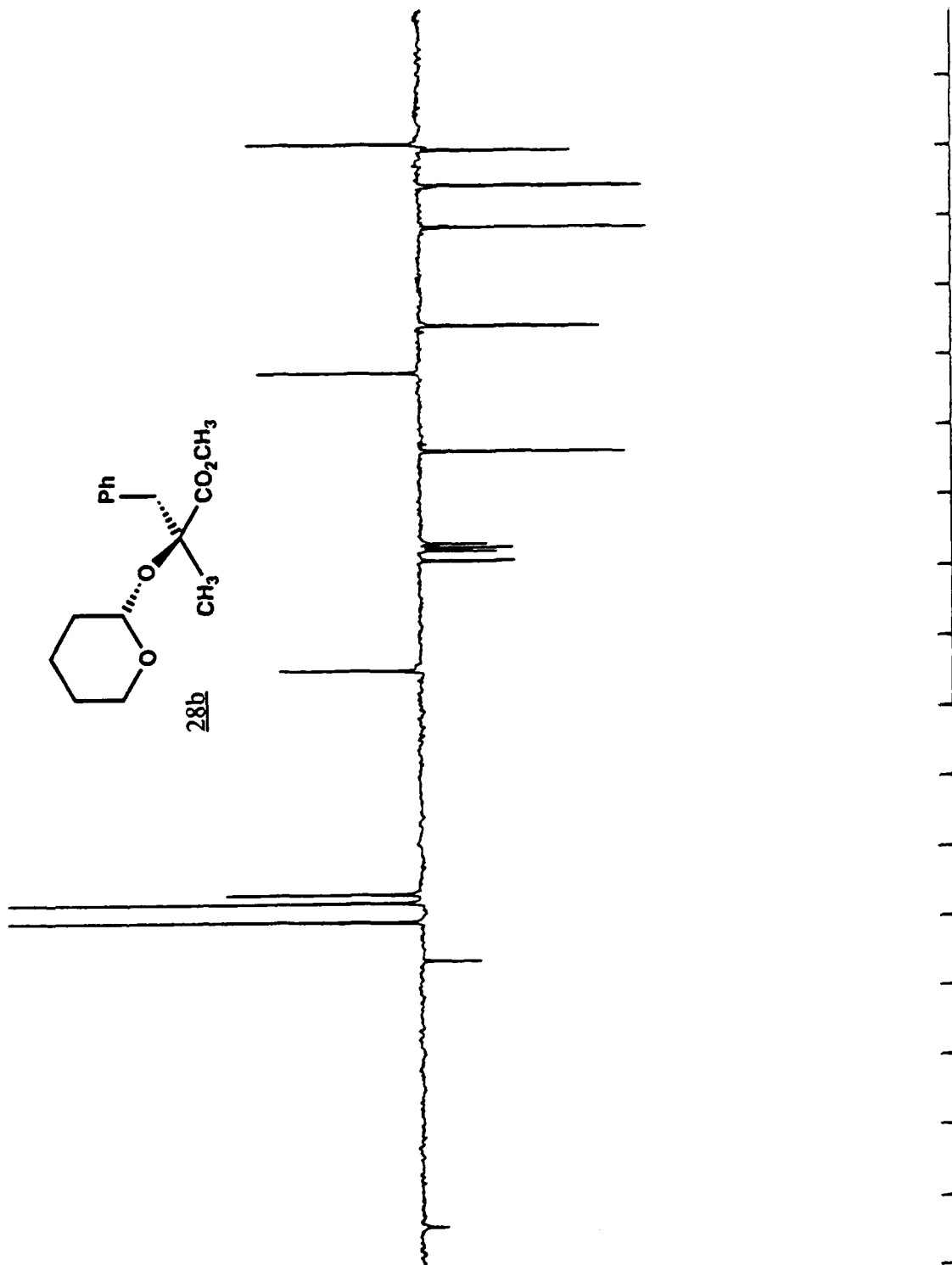
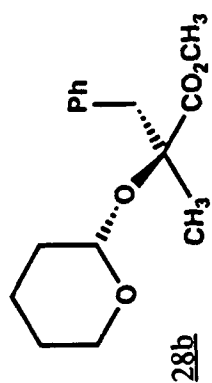


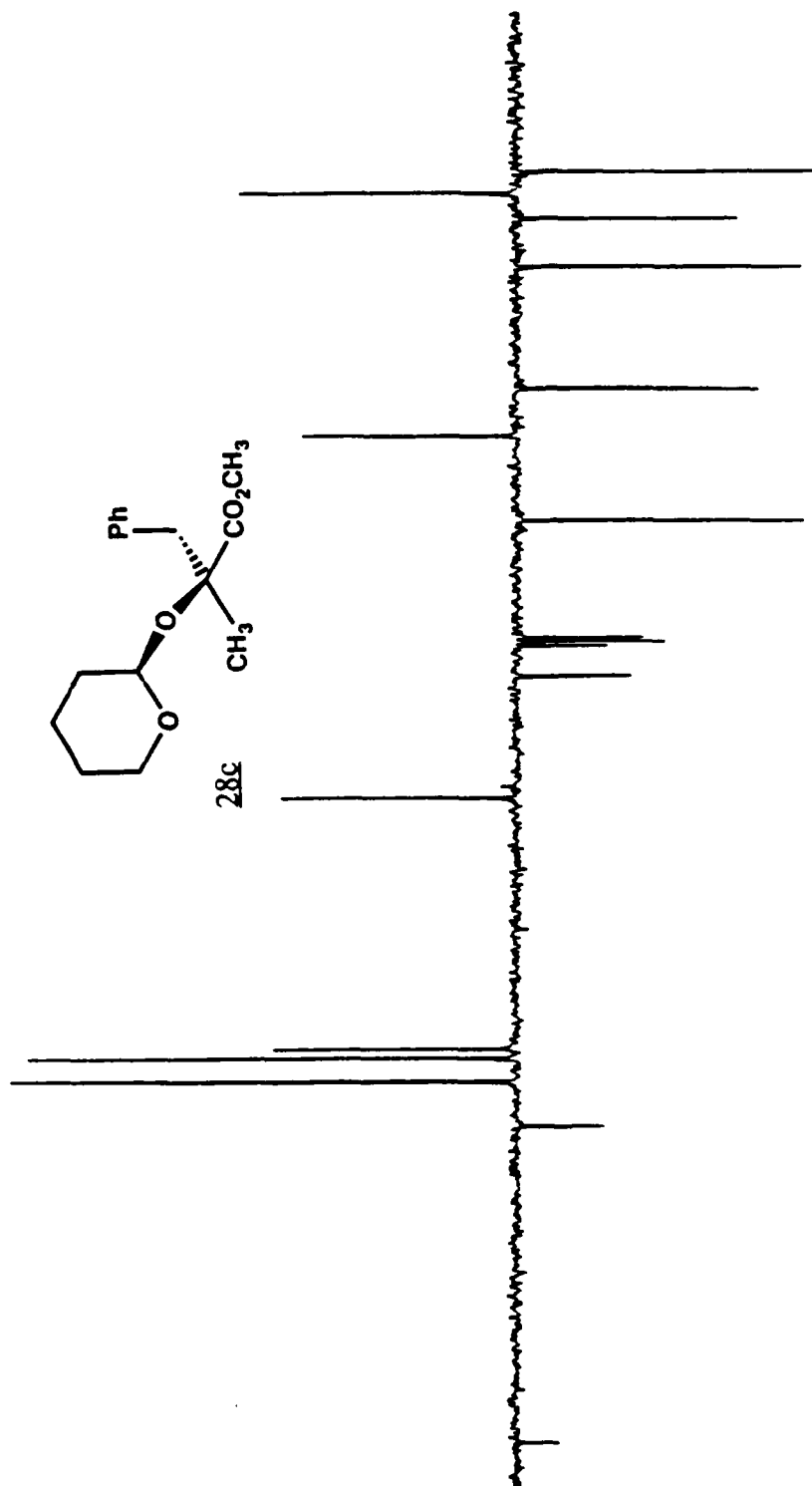


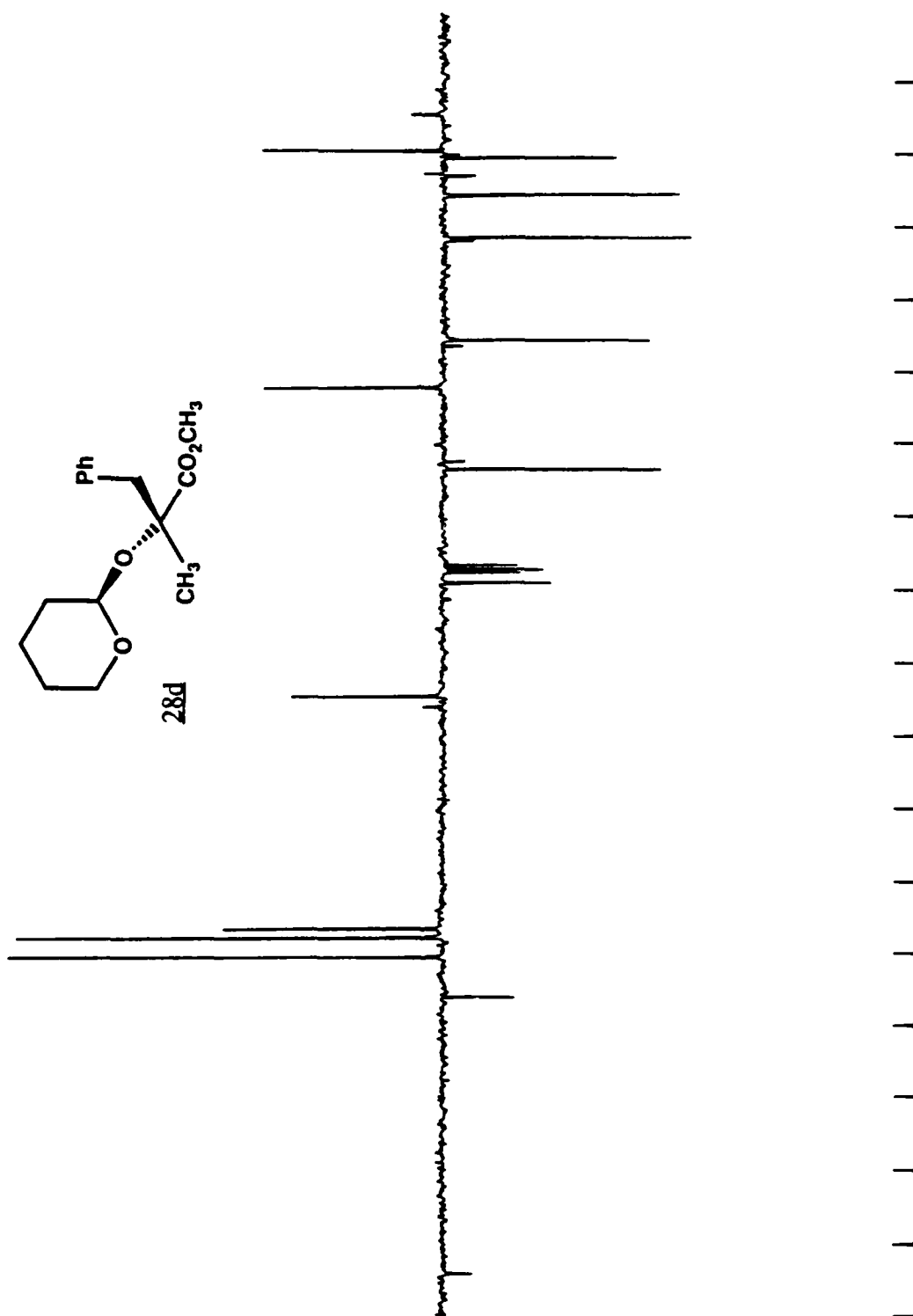


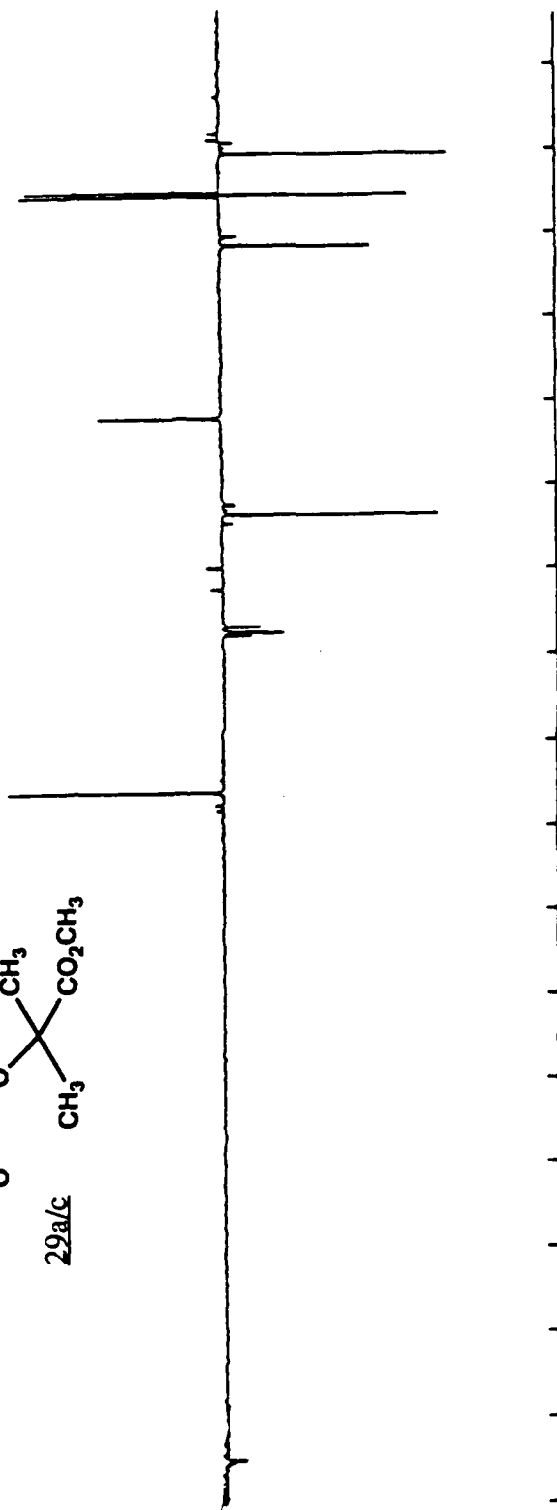
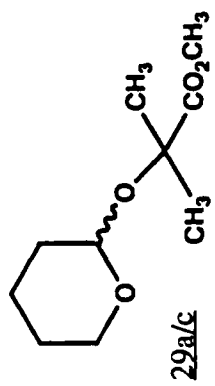


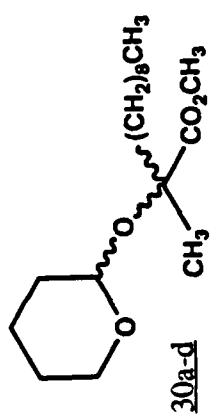


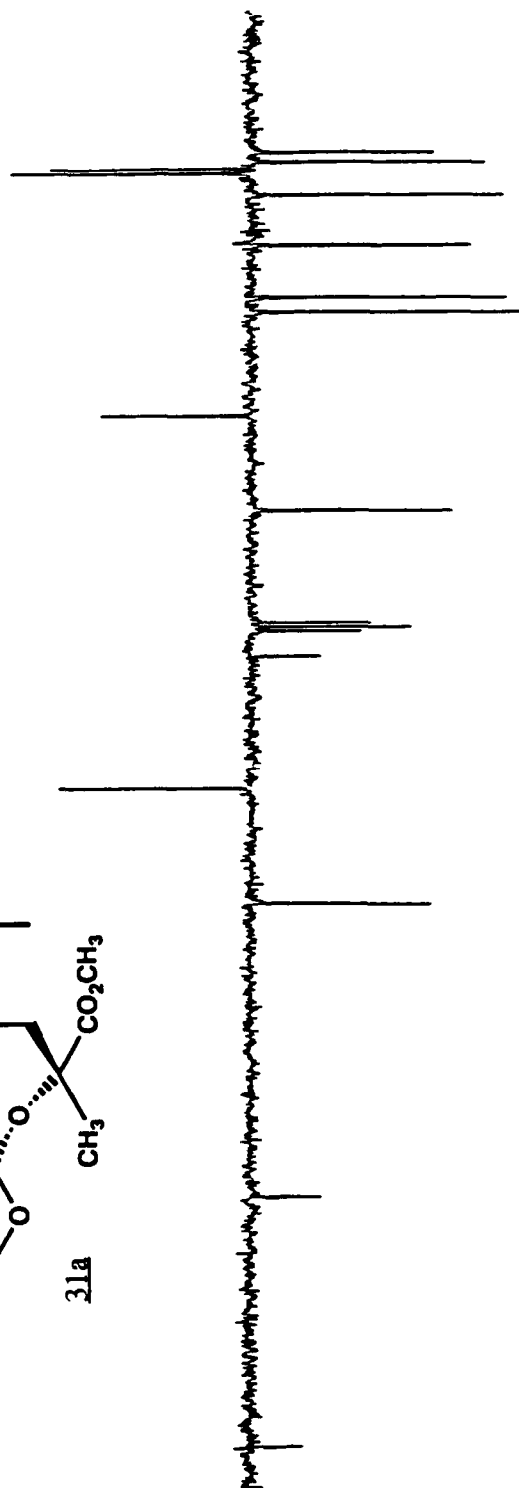
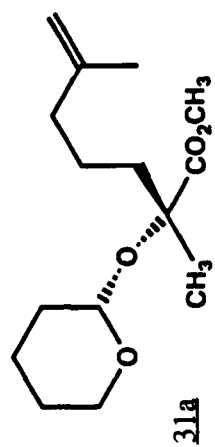


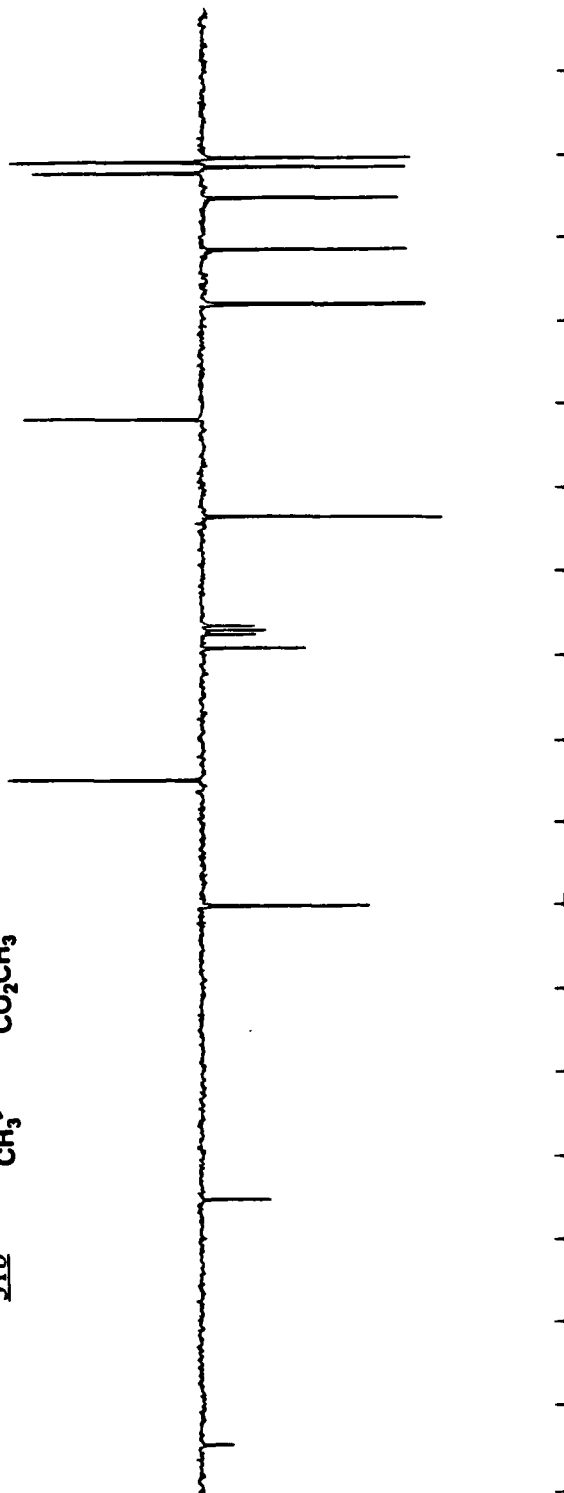
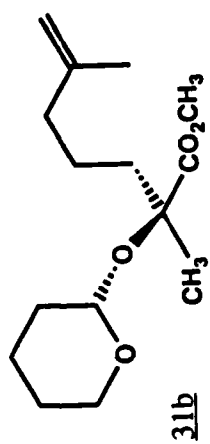


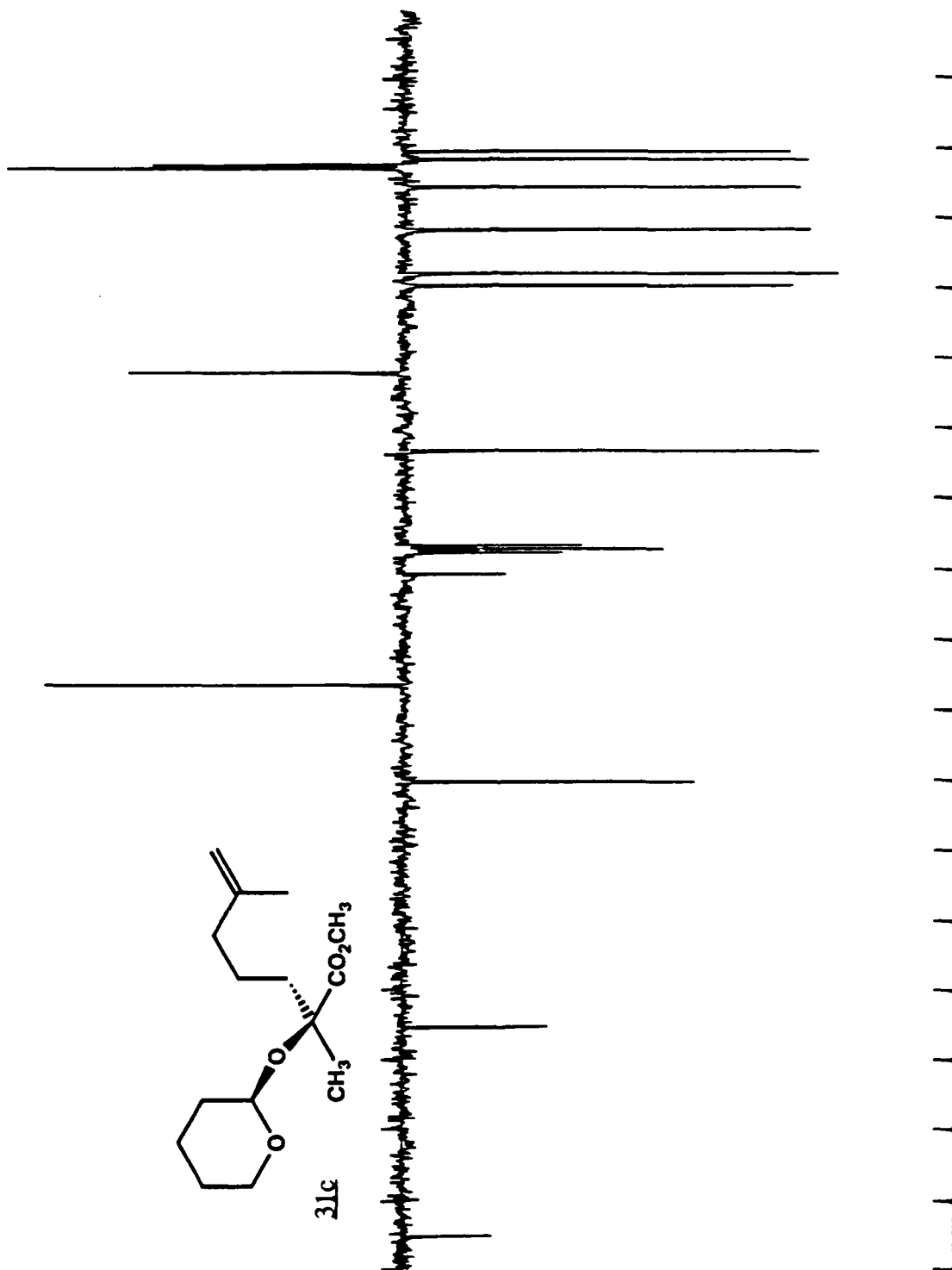
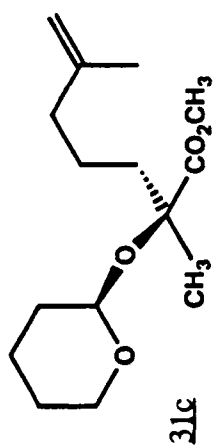


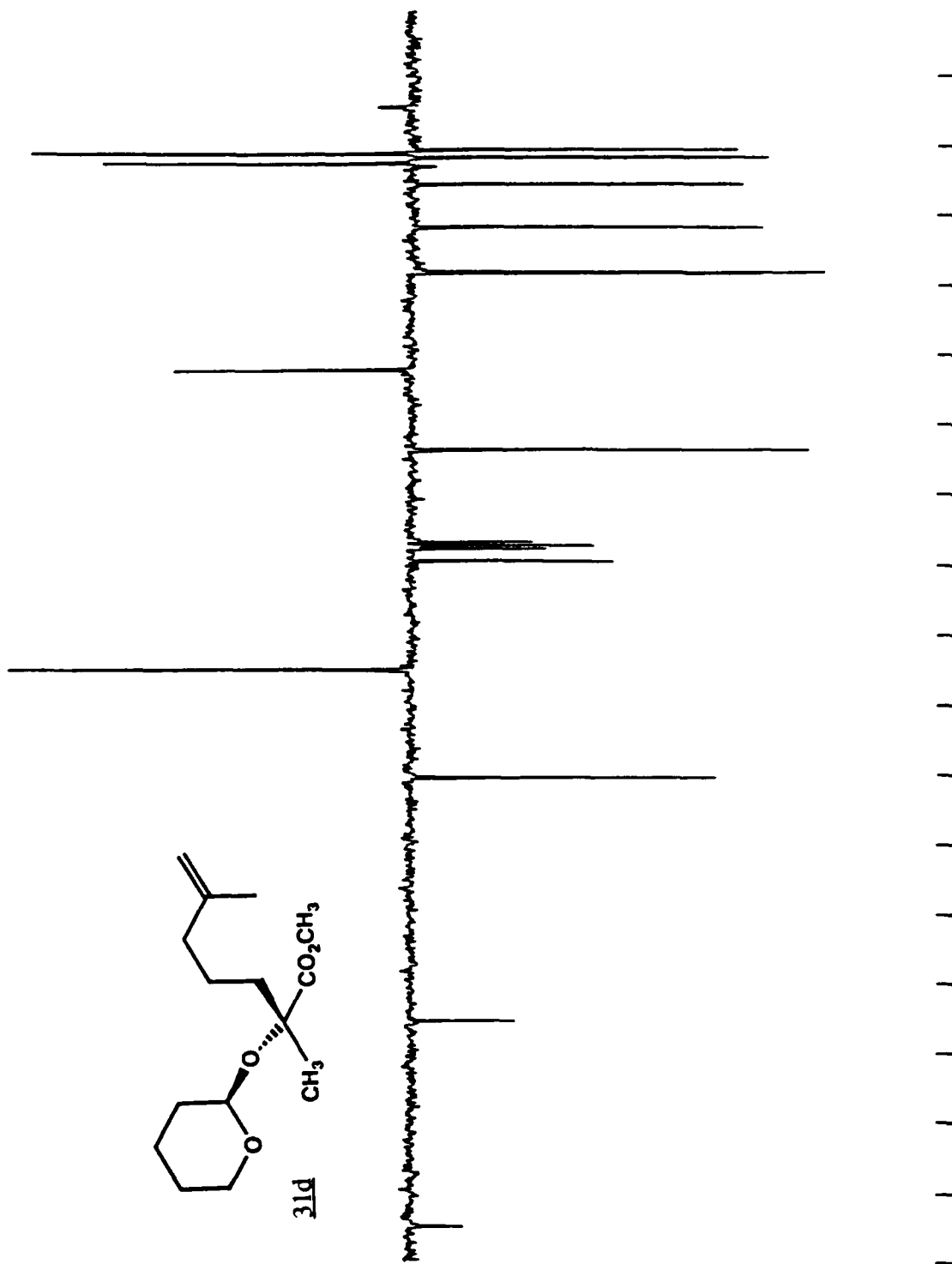


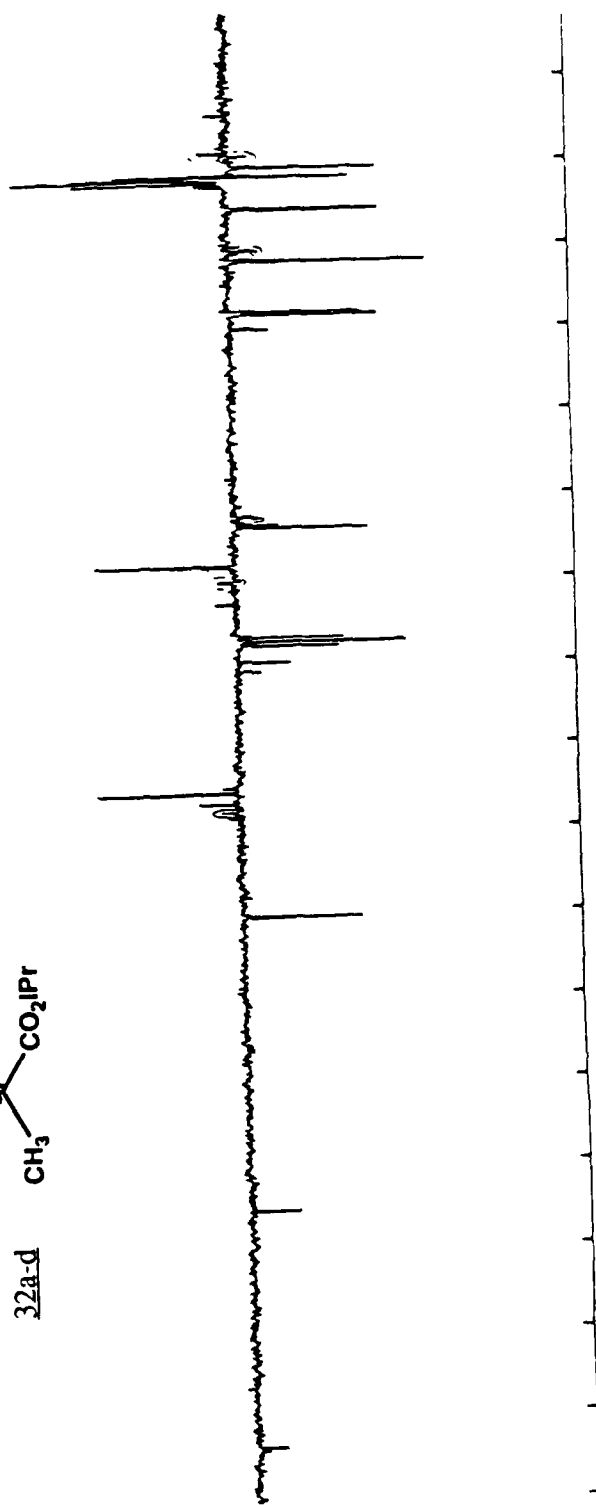
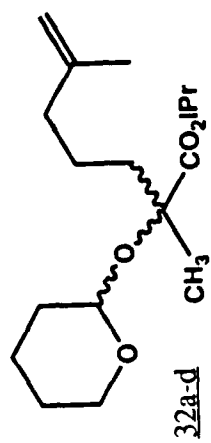


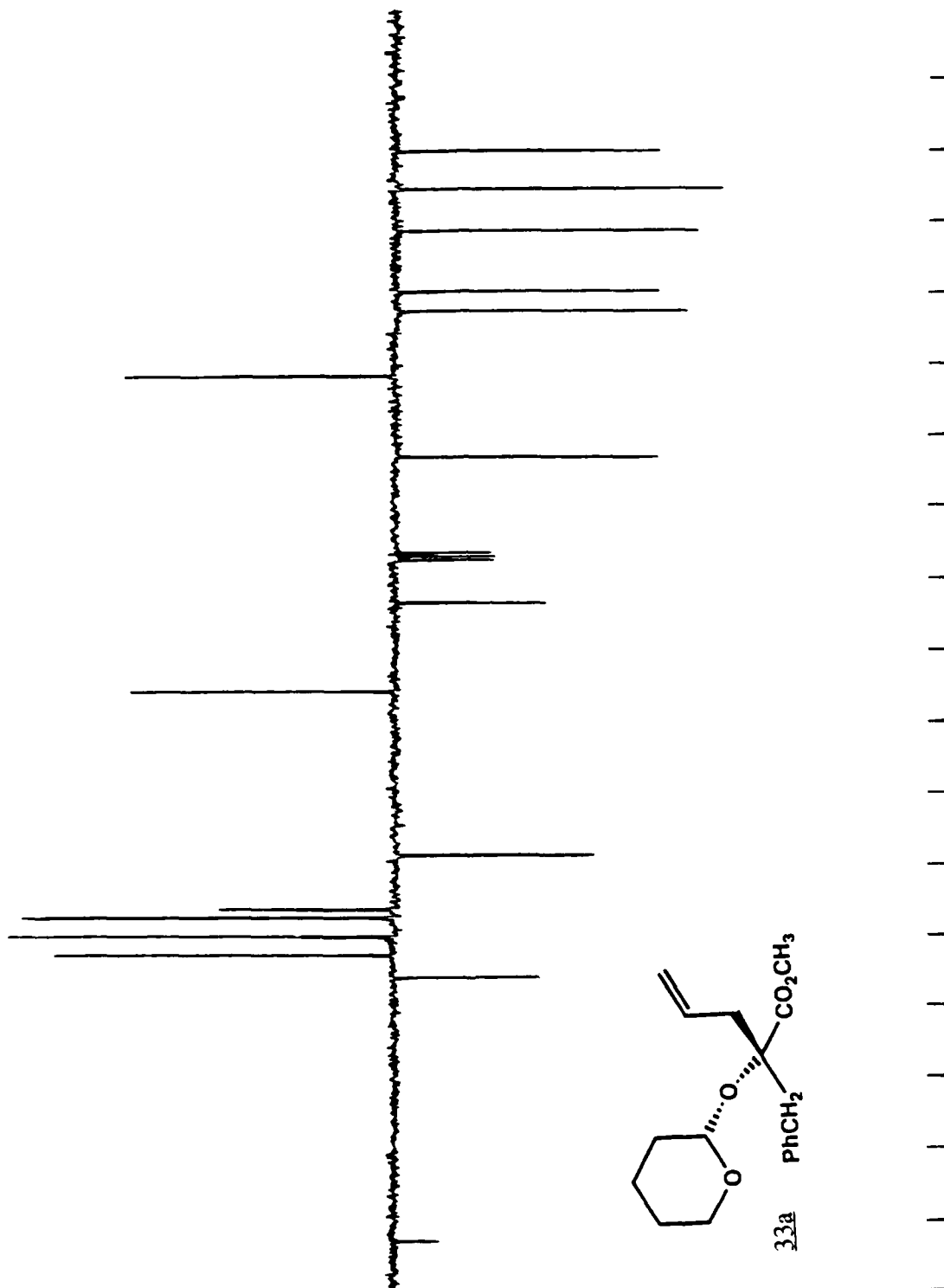


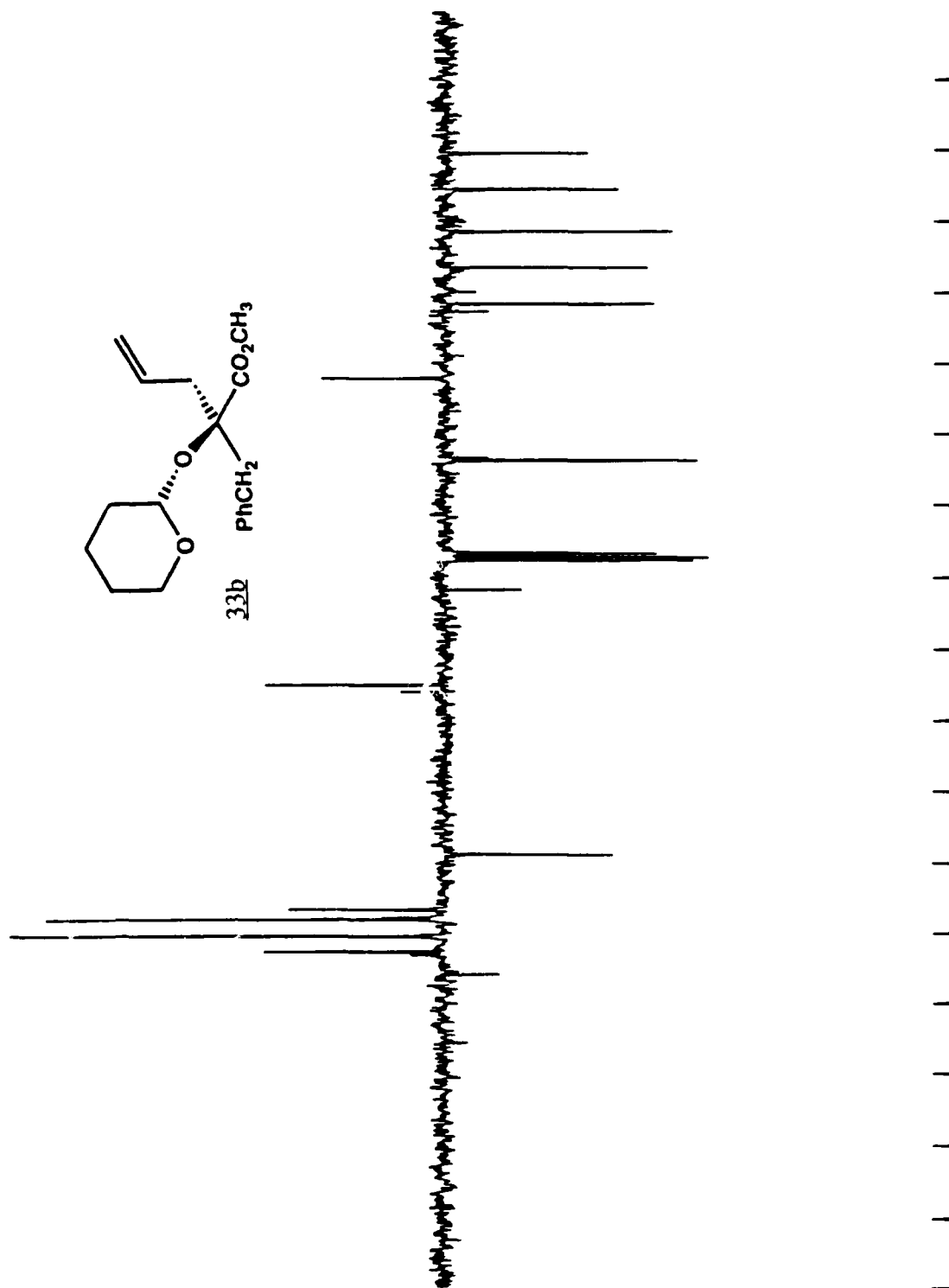


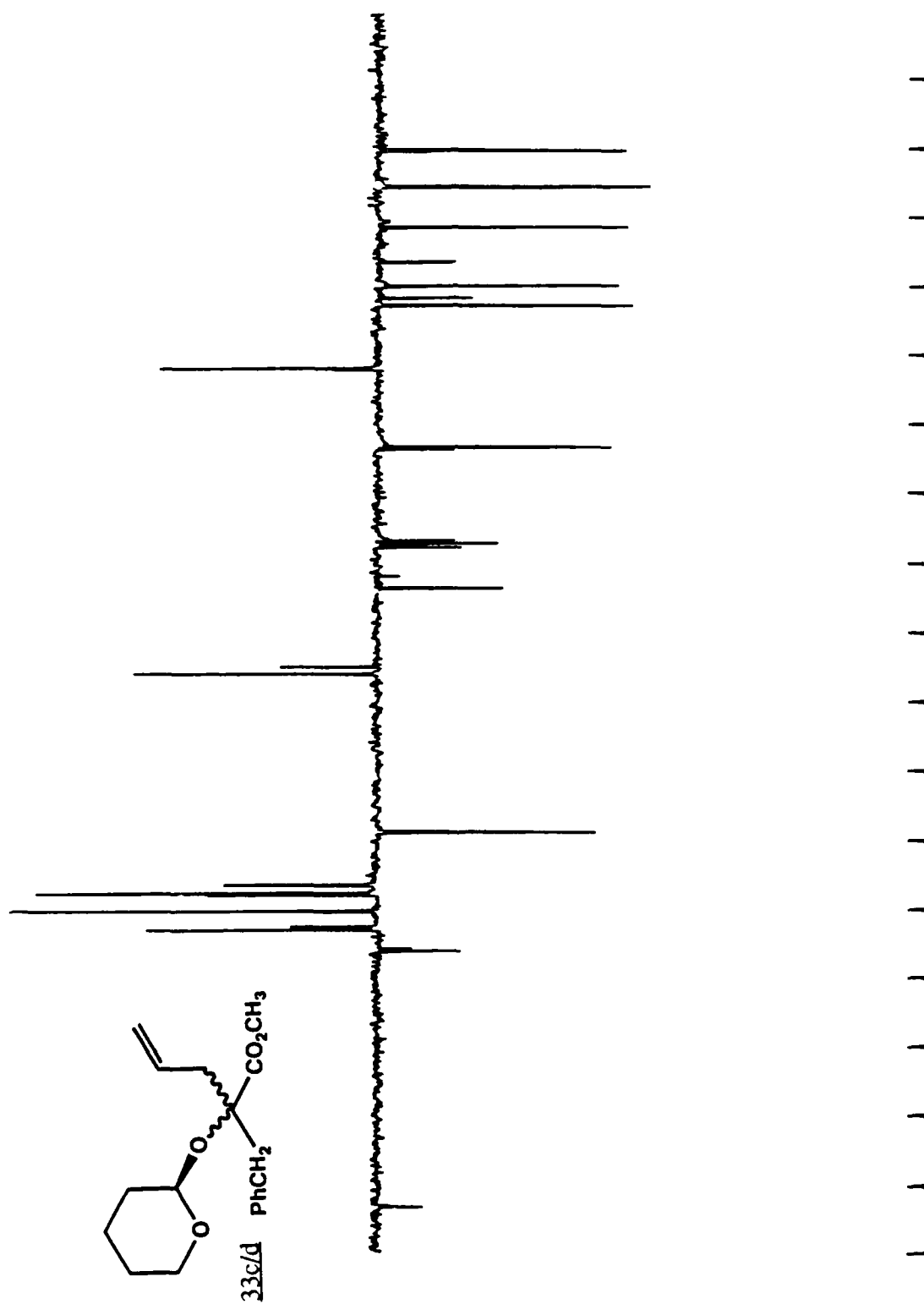


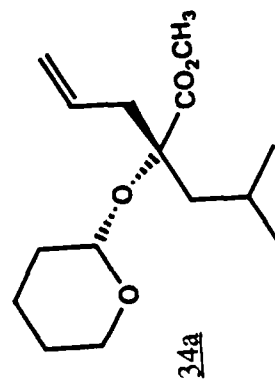
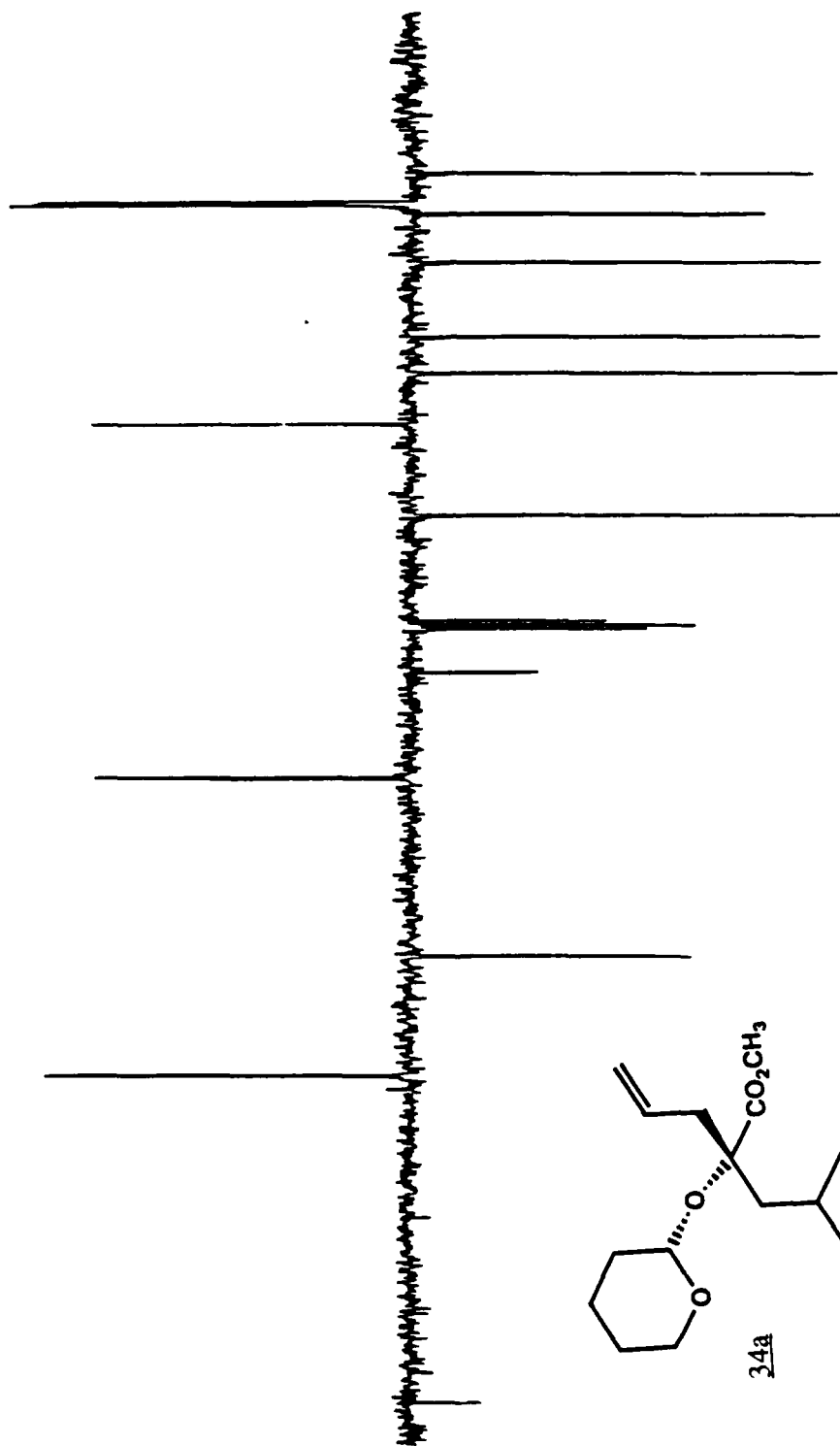


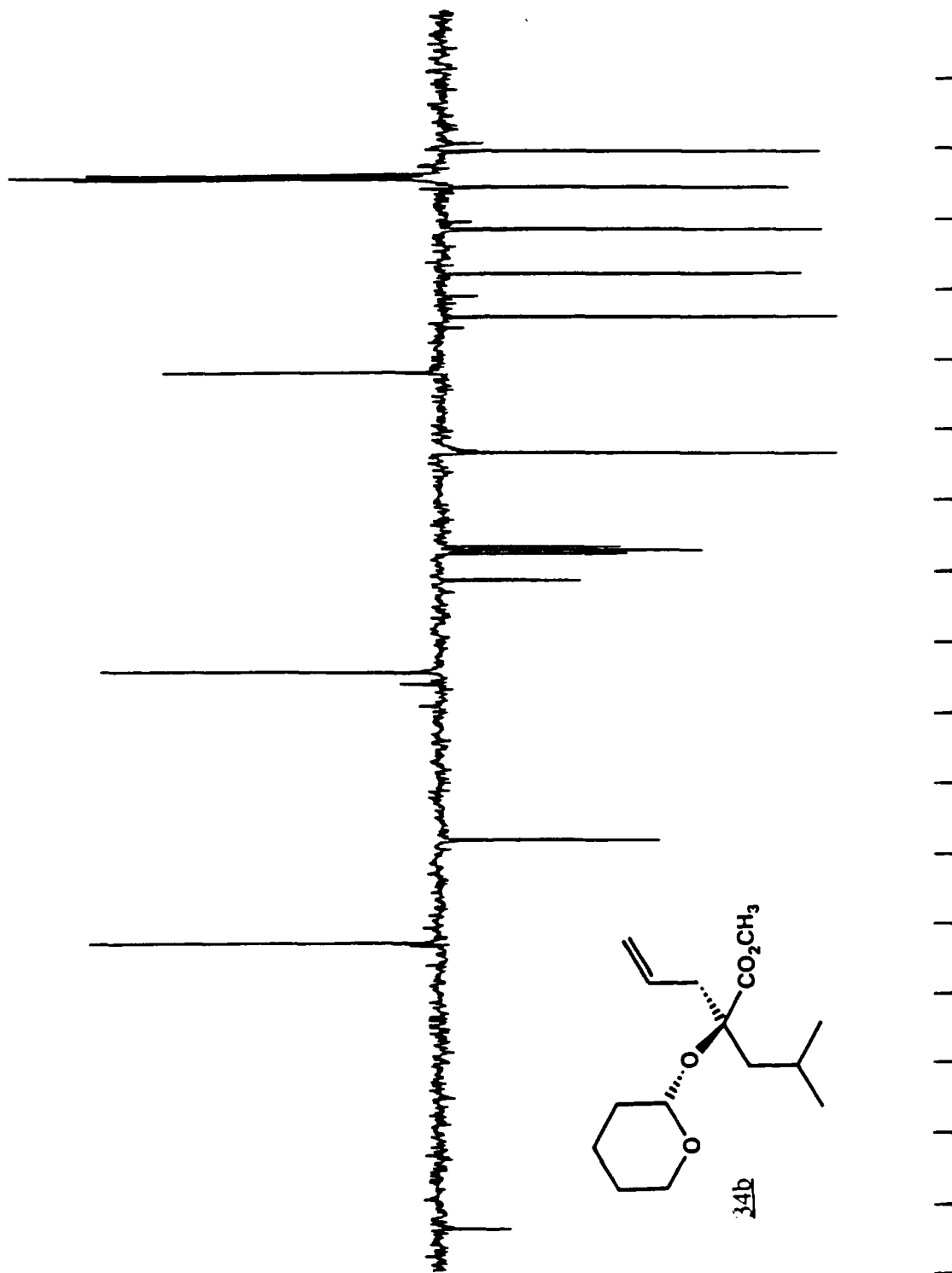


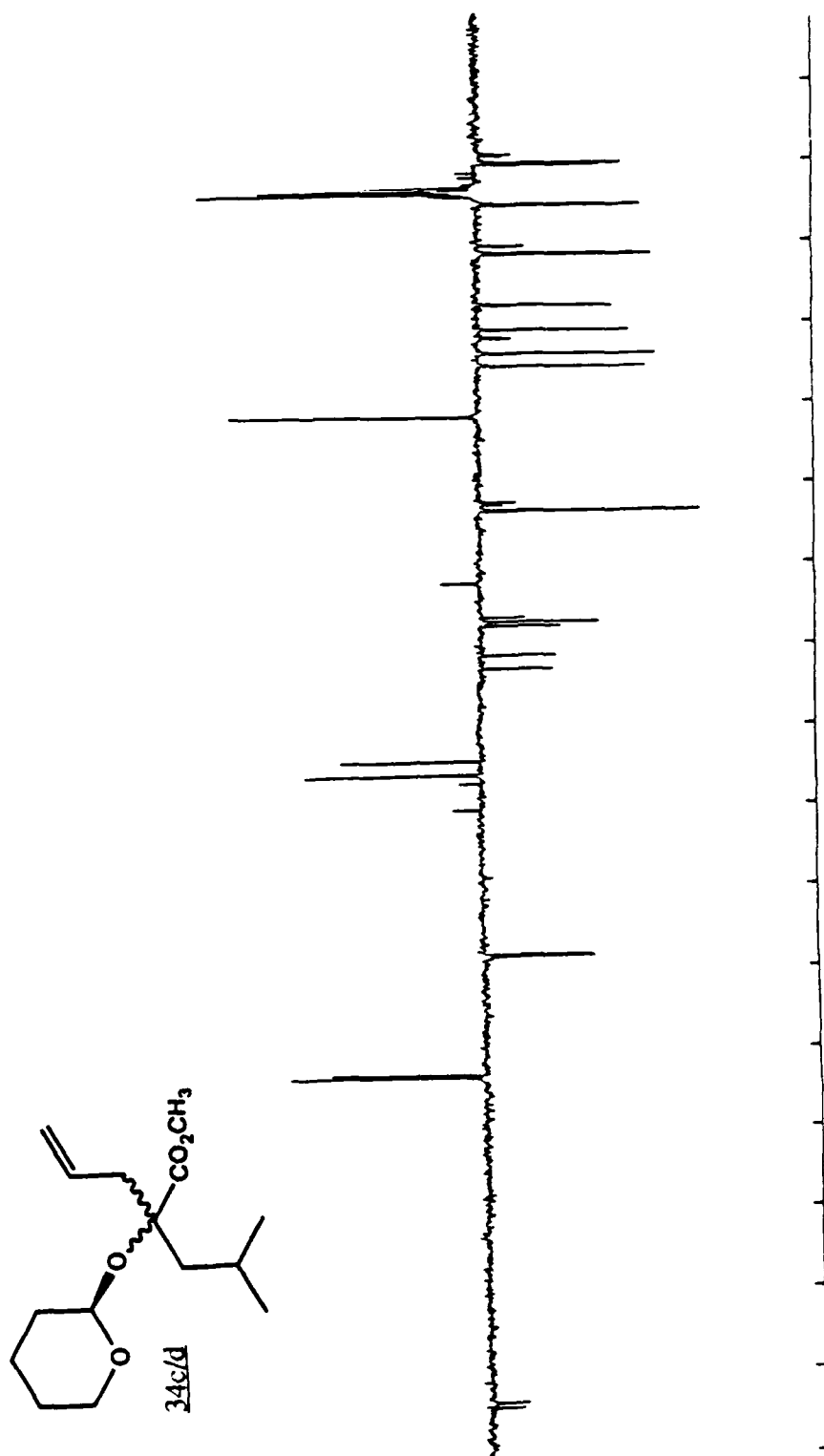


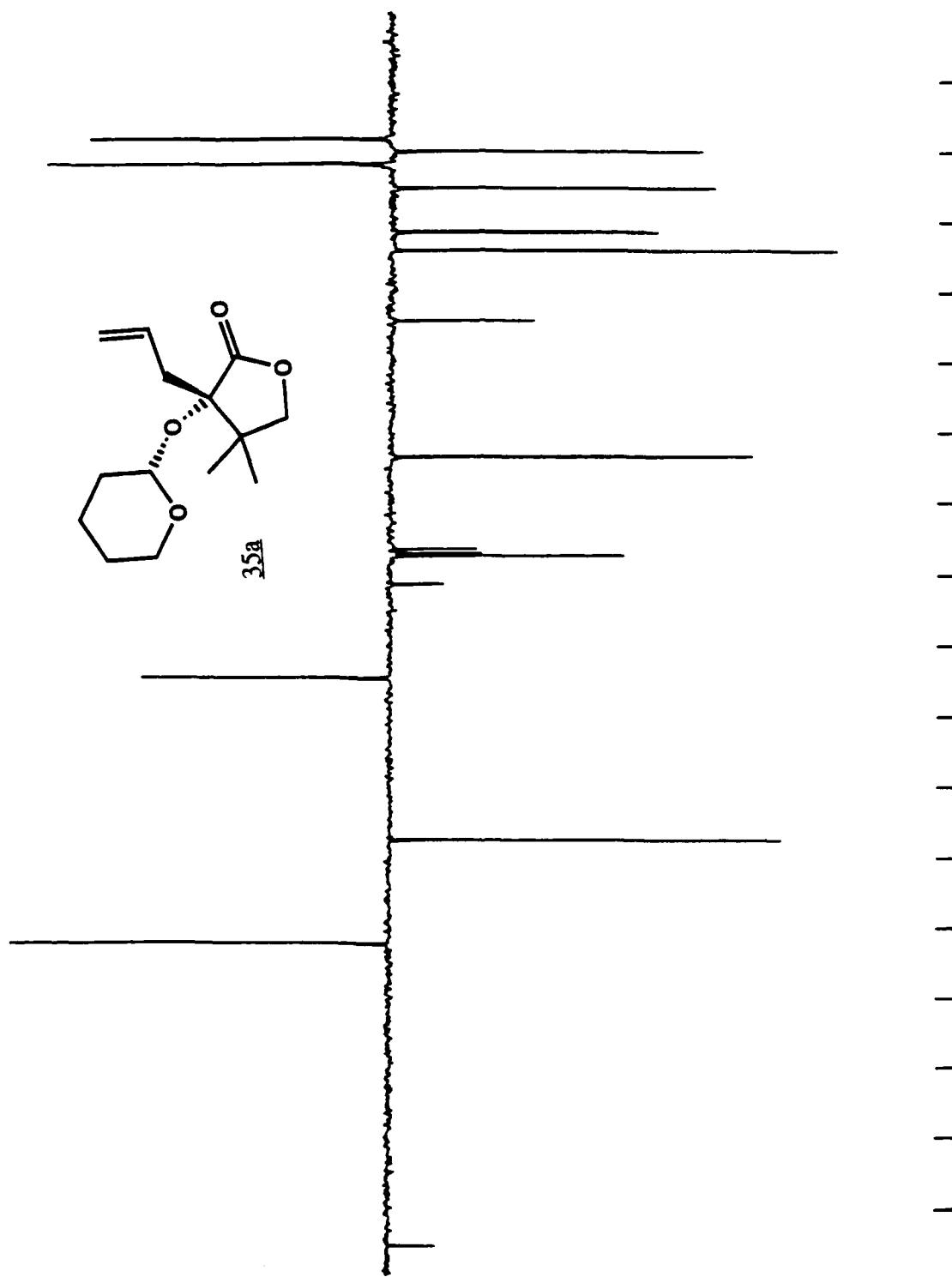


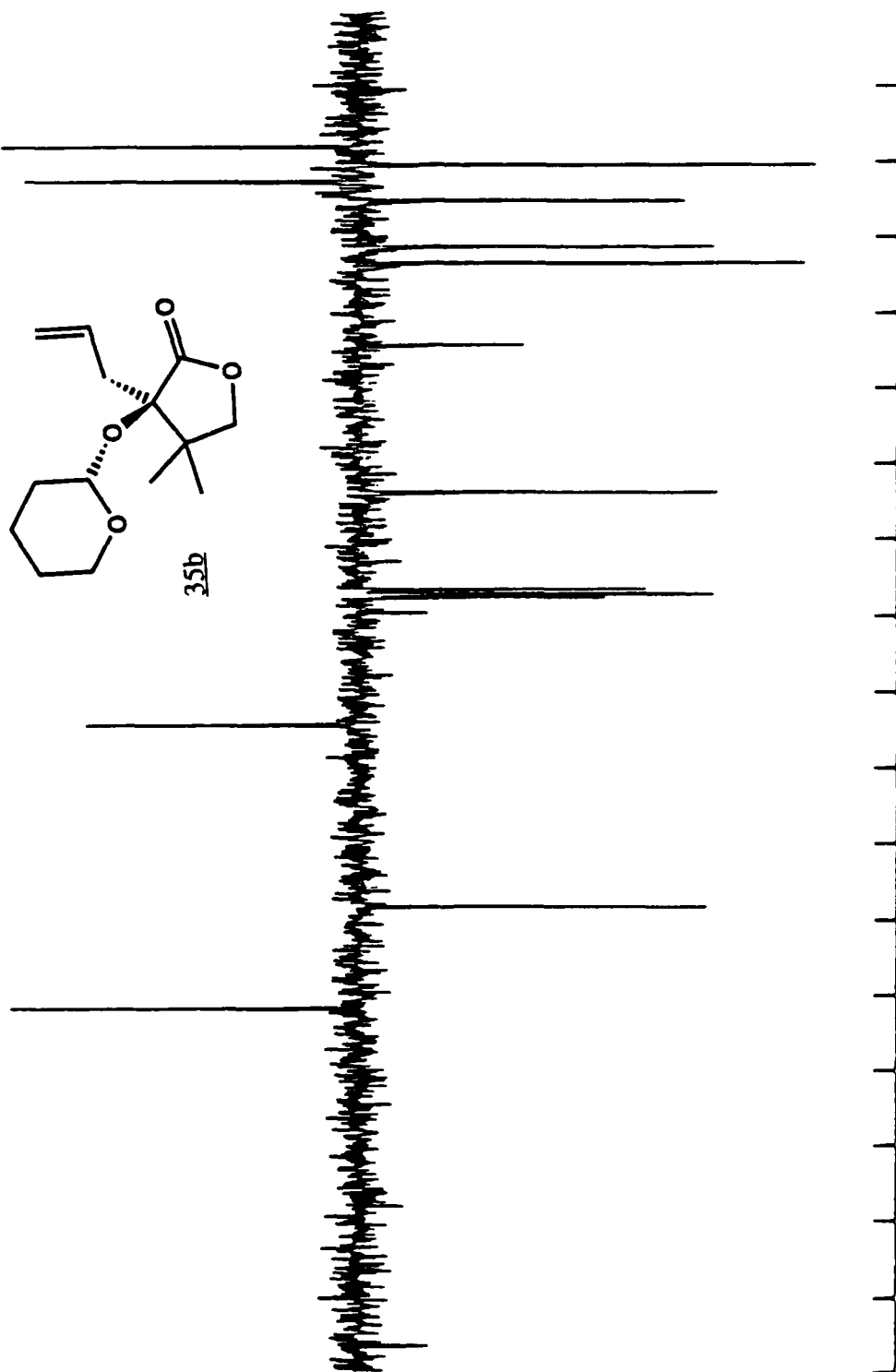


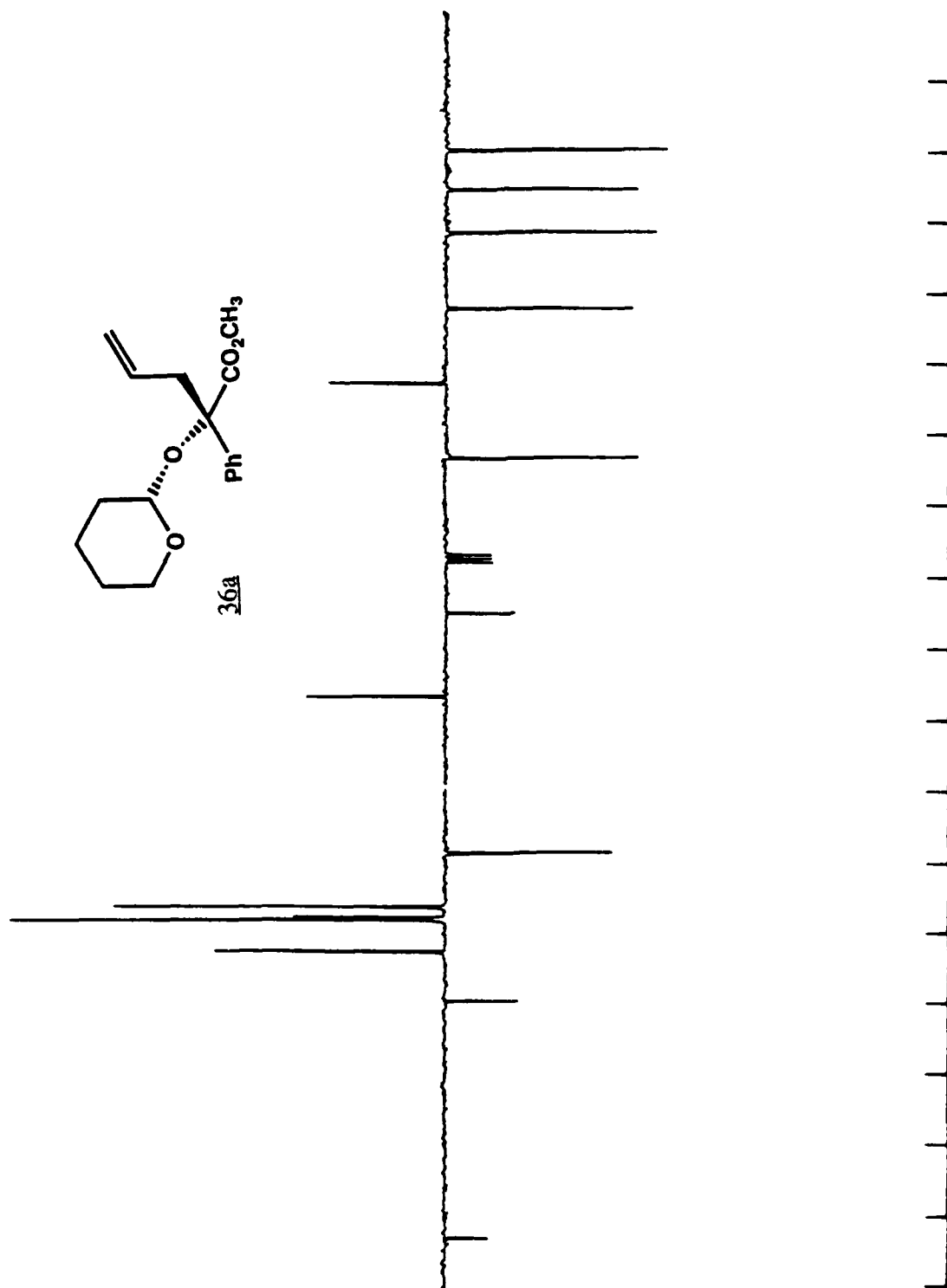


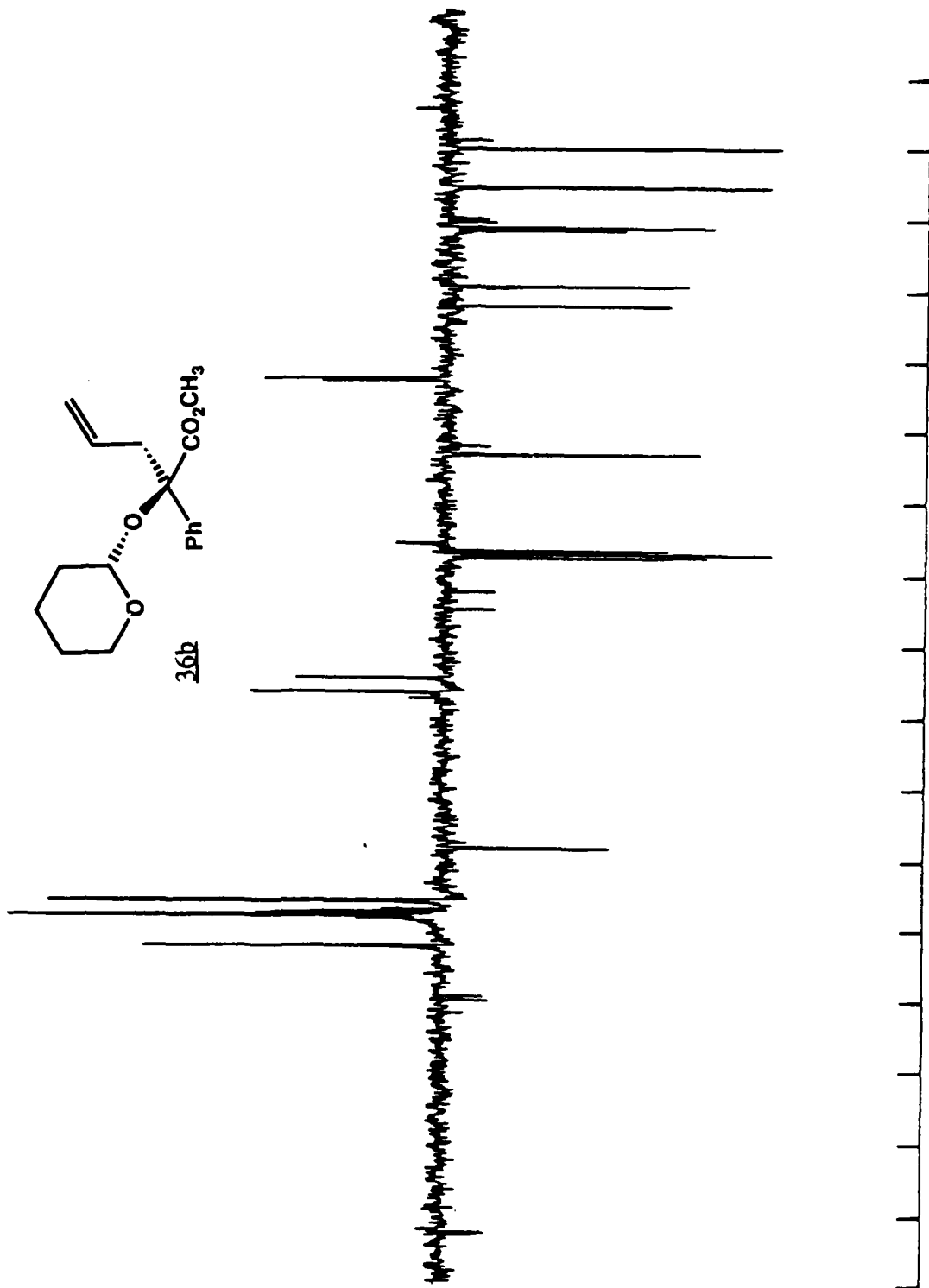
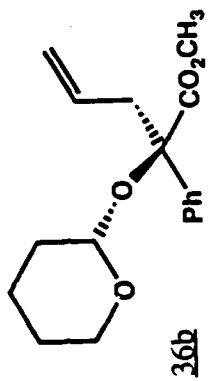


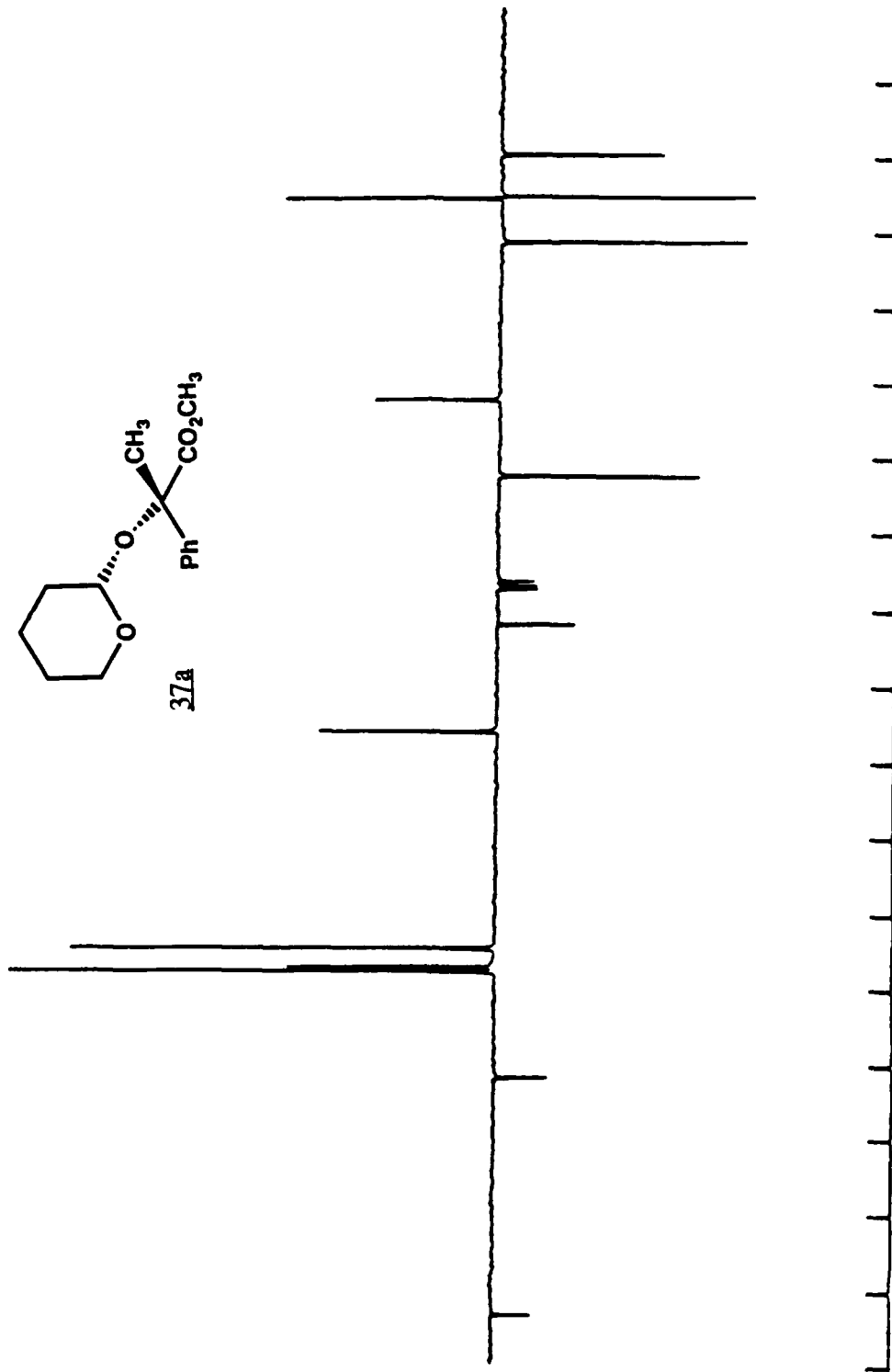
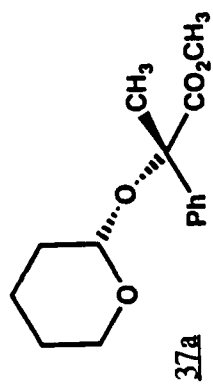


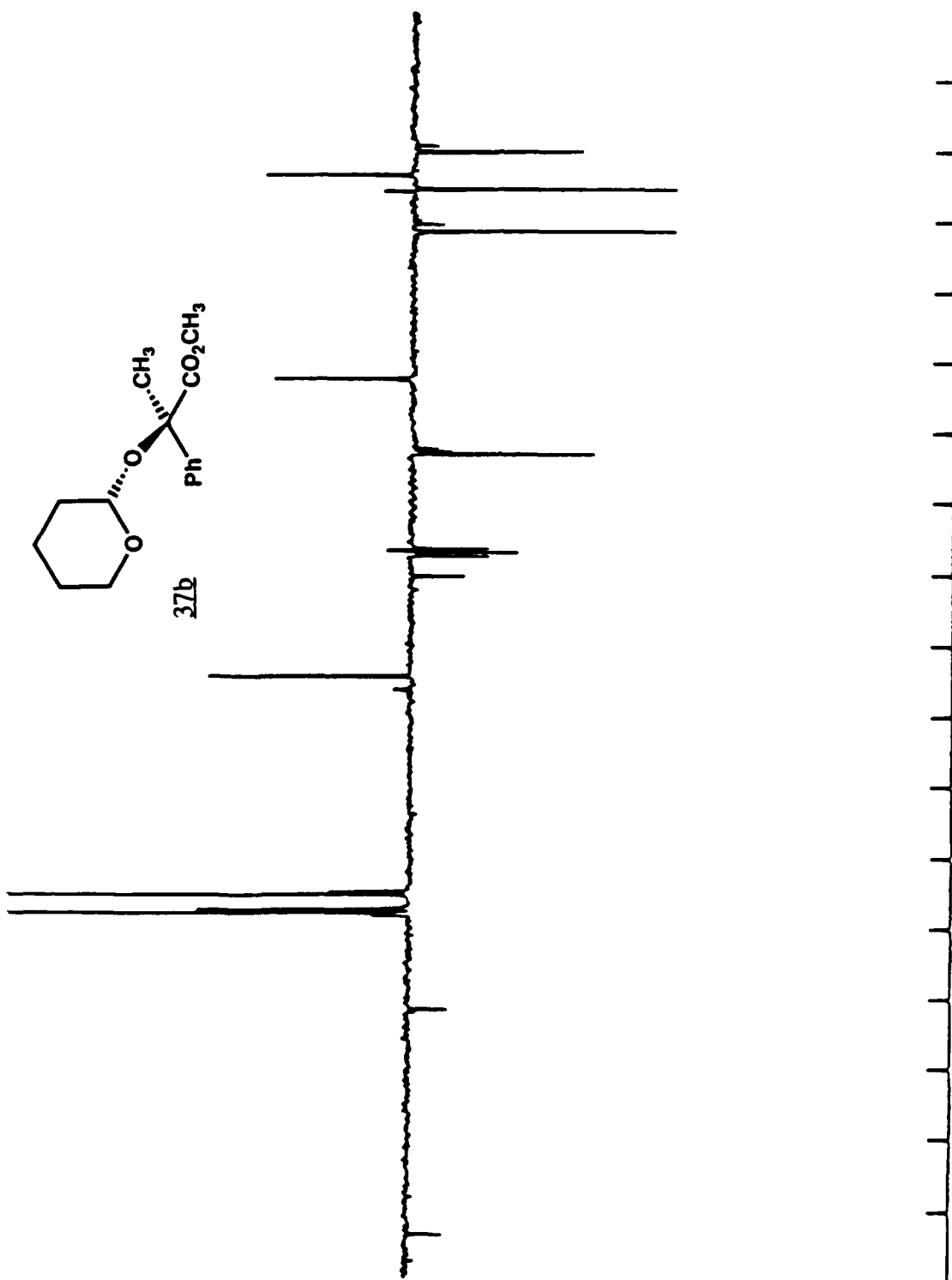


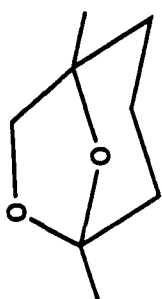




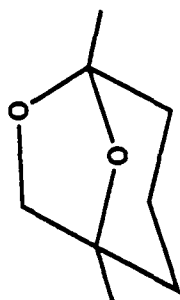




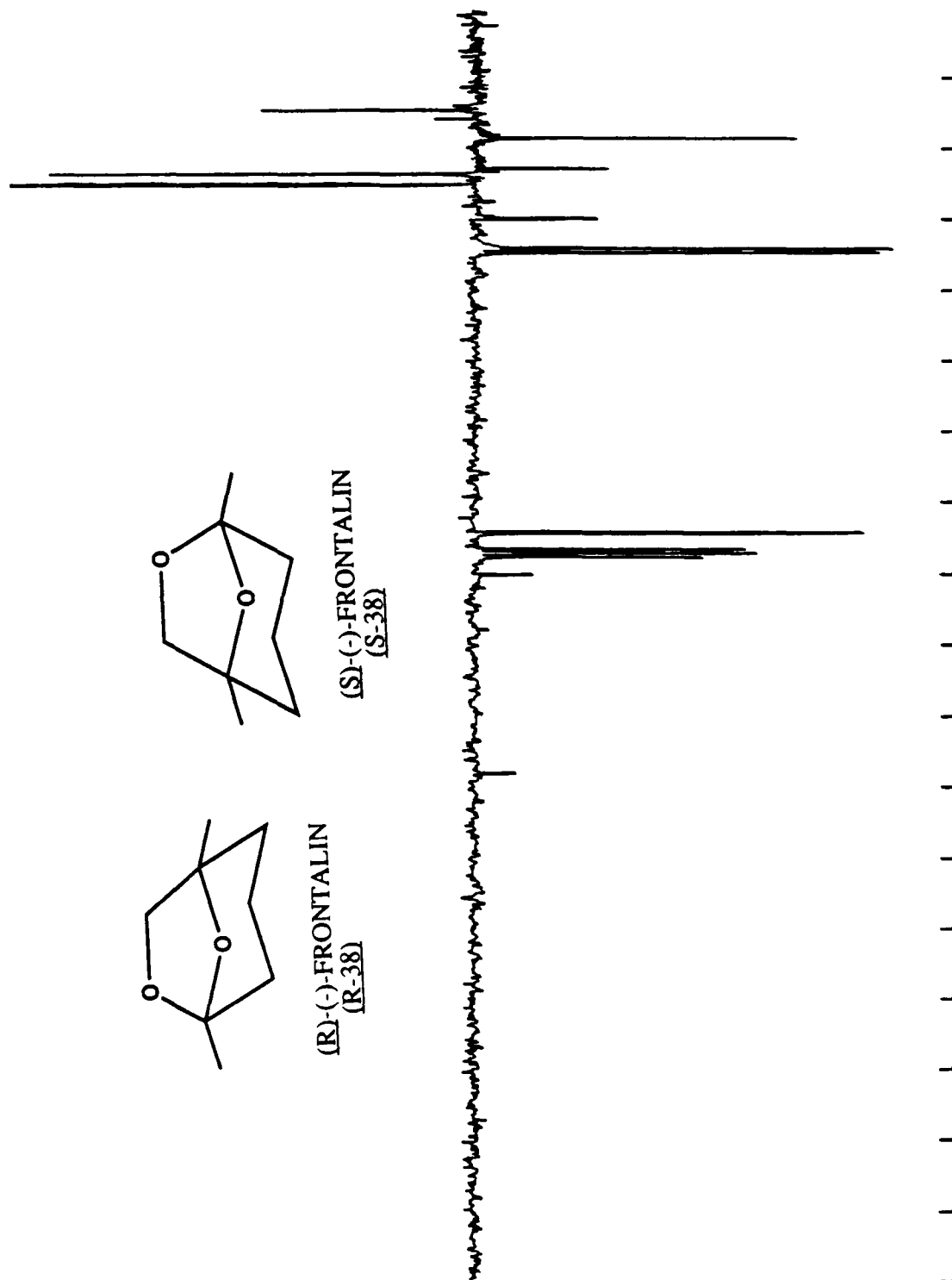


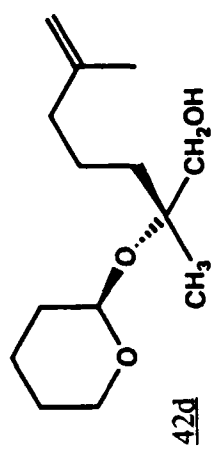


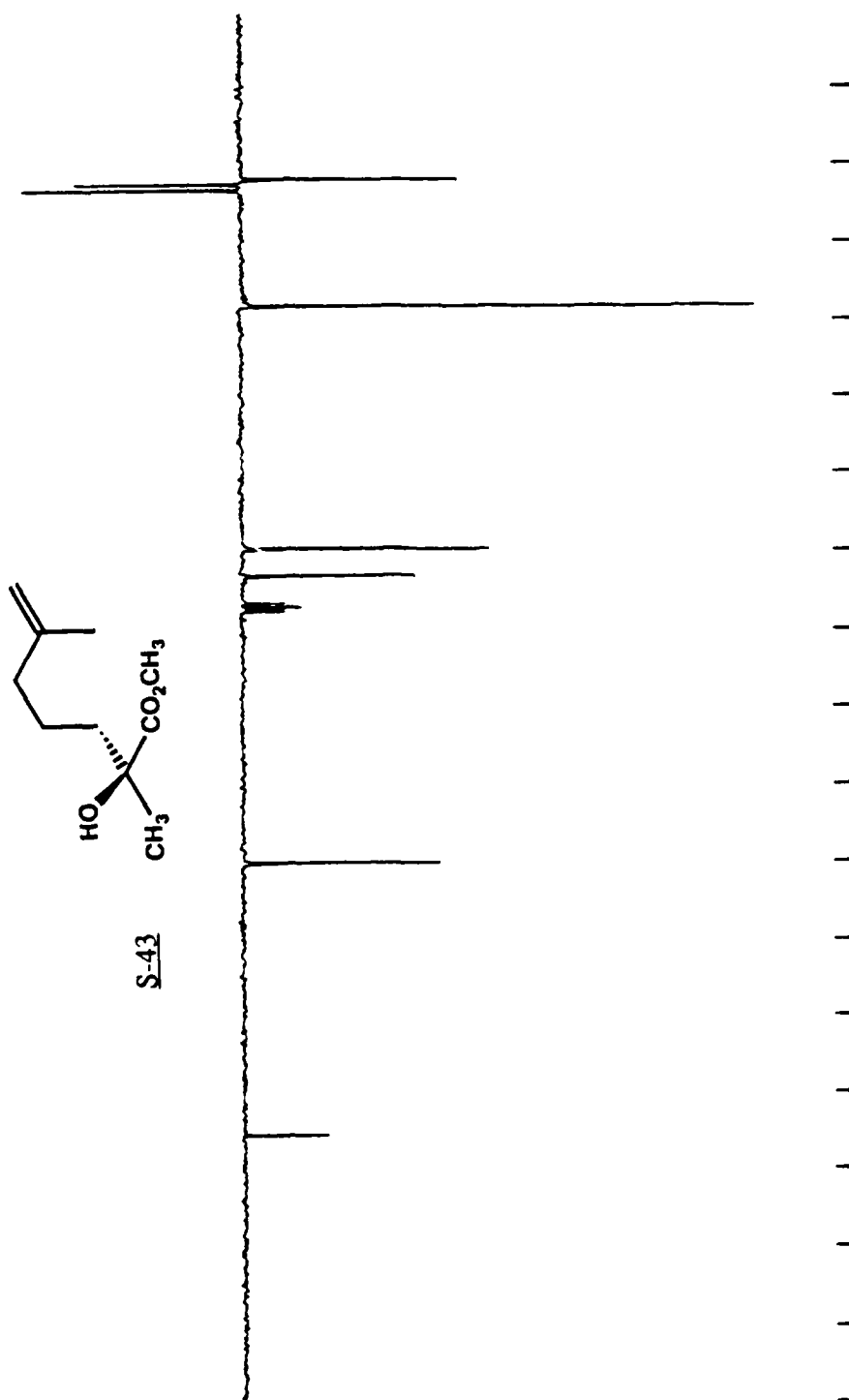
(R)-(-)-FRONTALIN
(R-38)

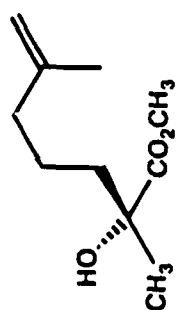


(S)-(-)-FRONTALIN
(S-38)

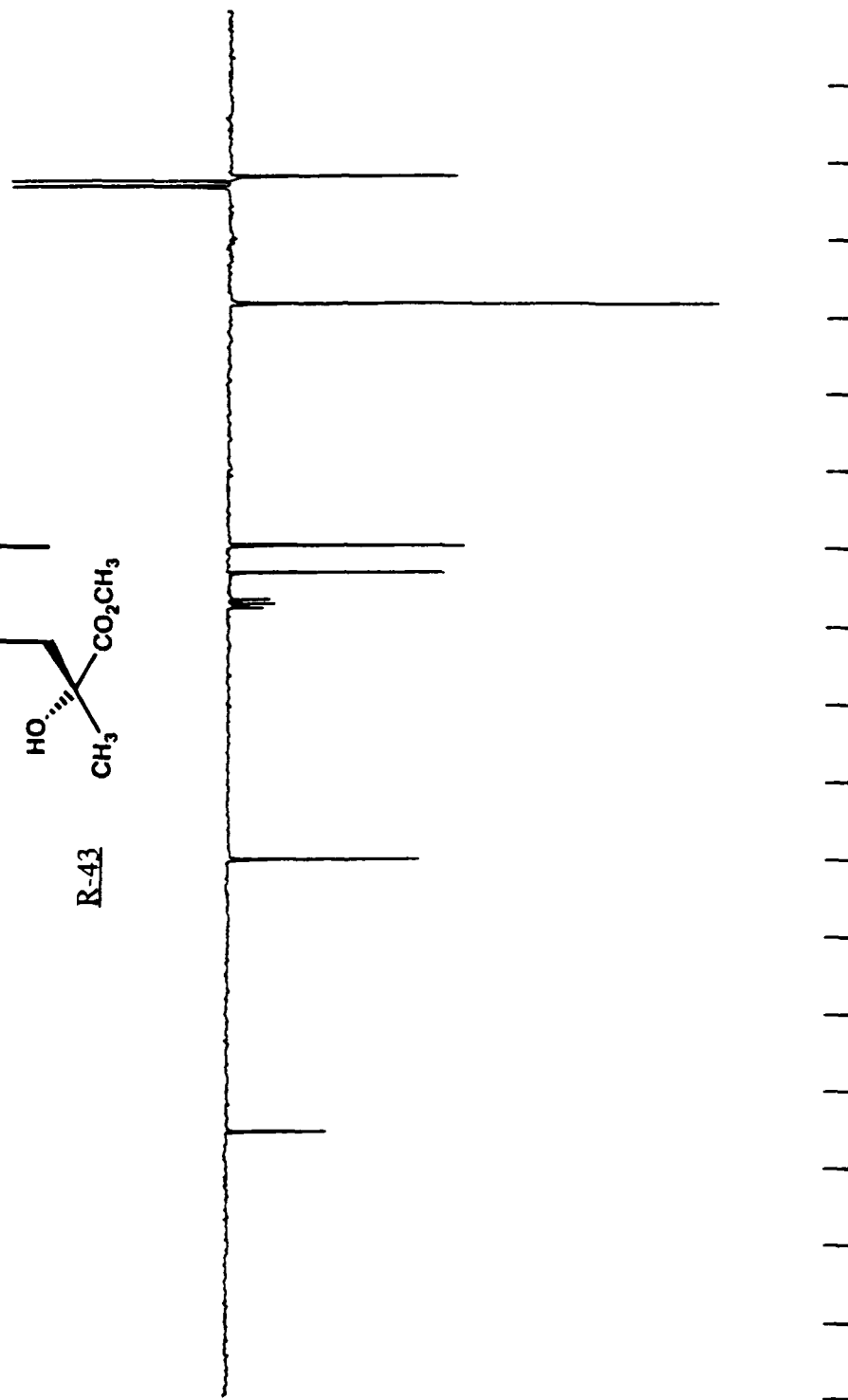


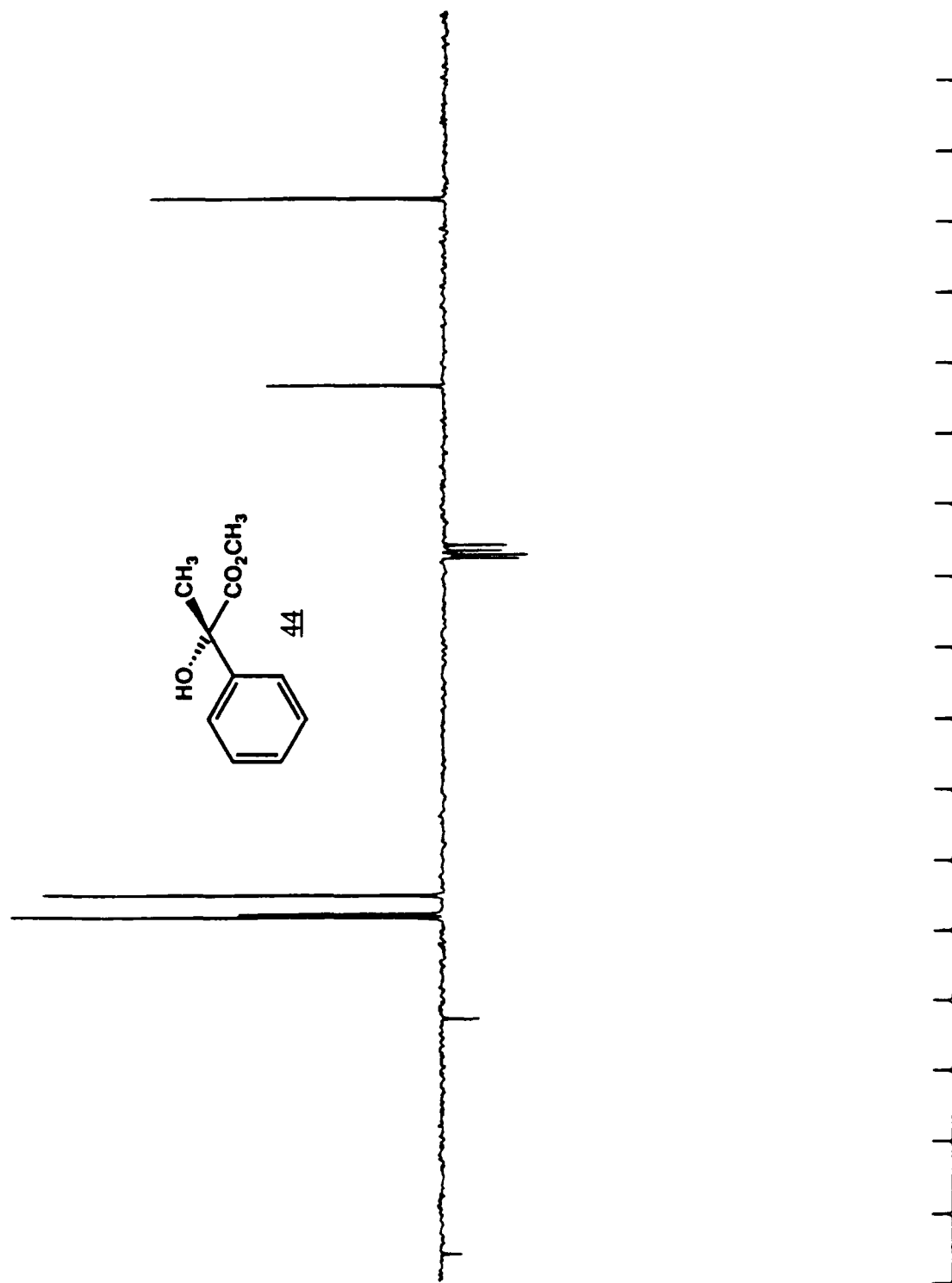


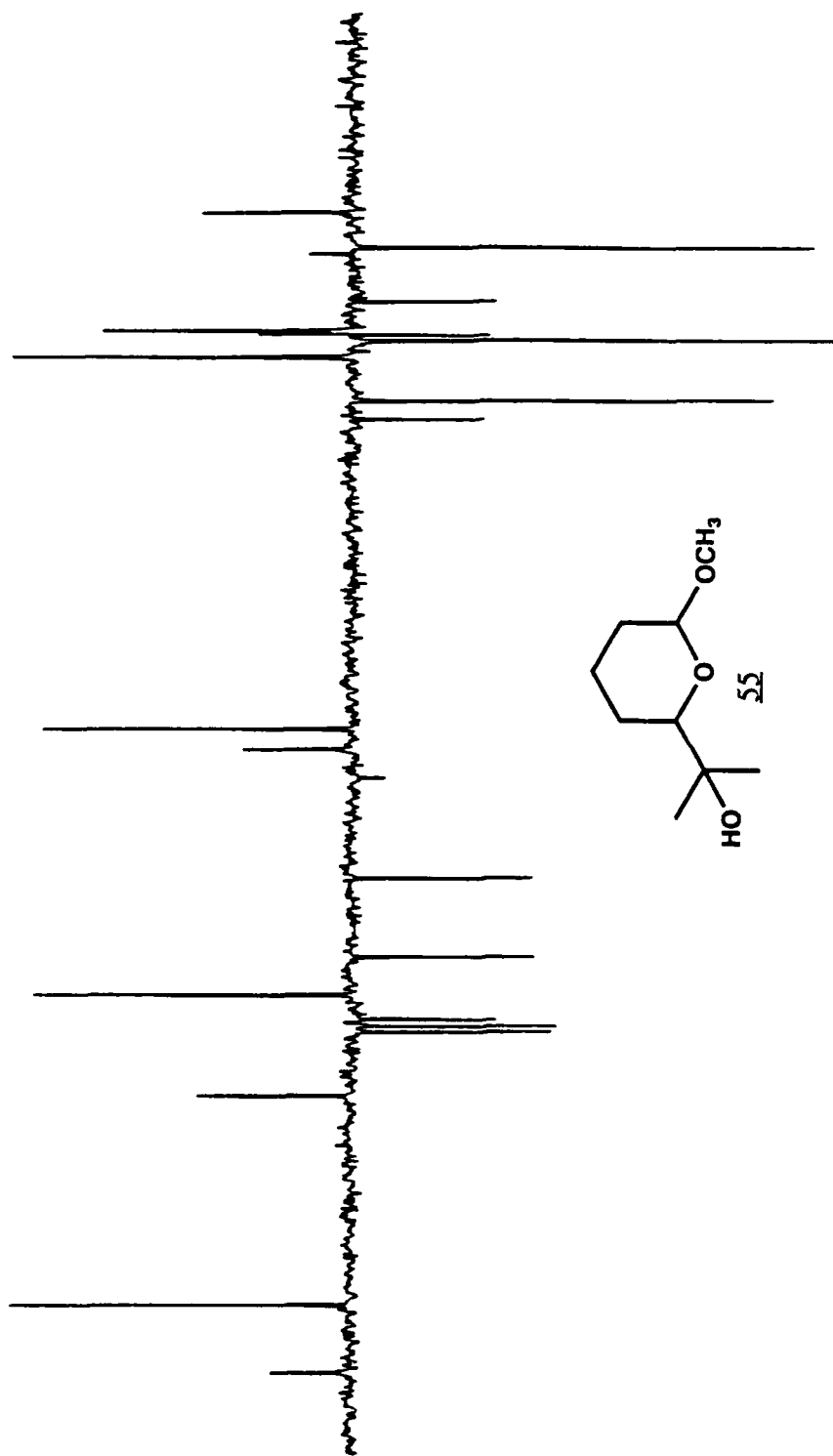


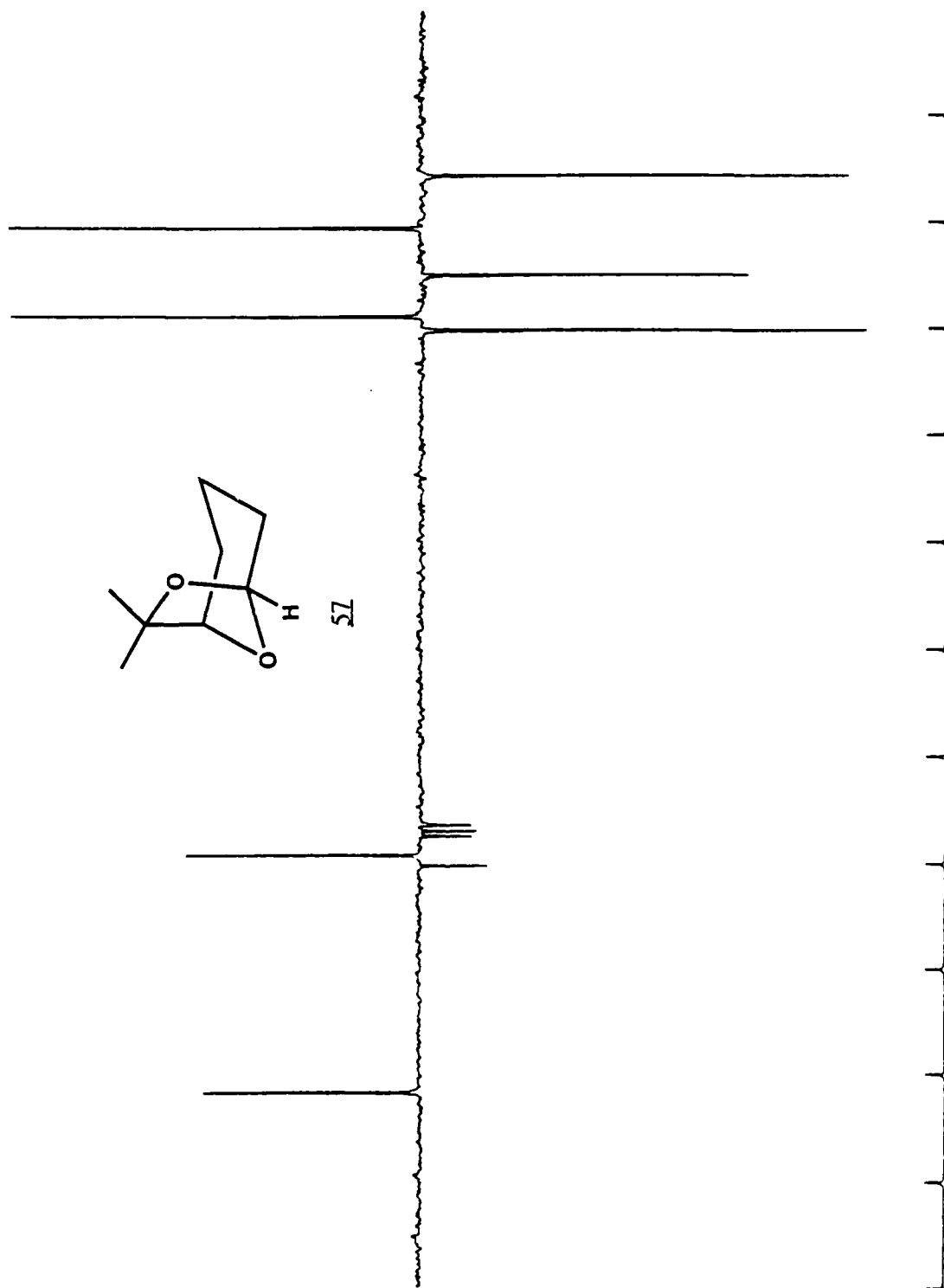


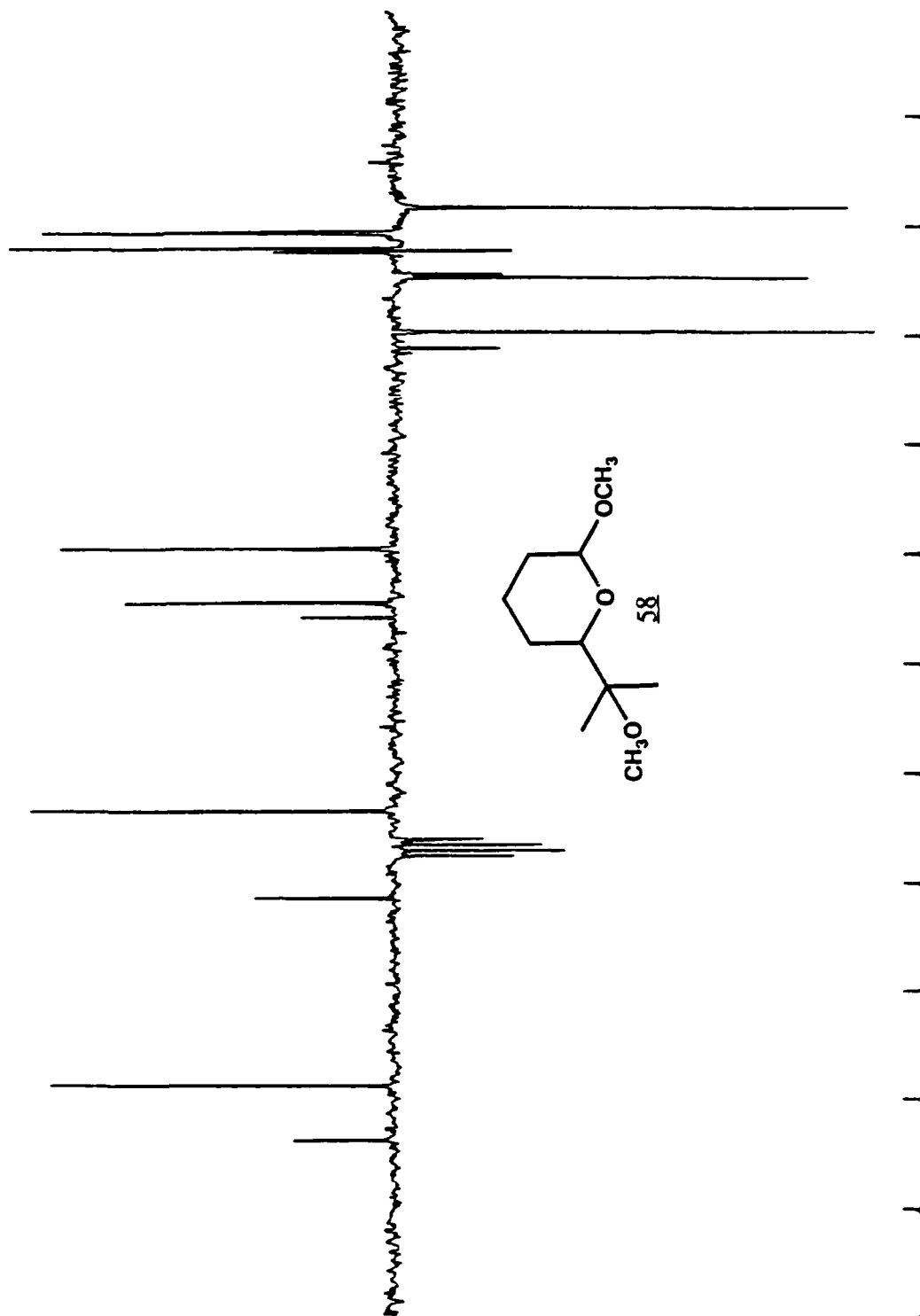
R-43

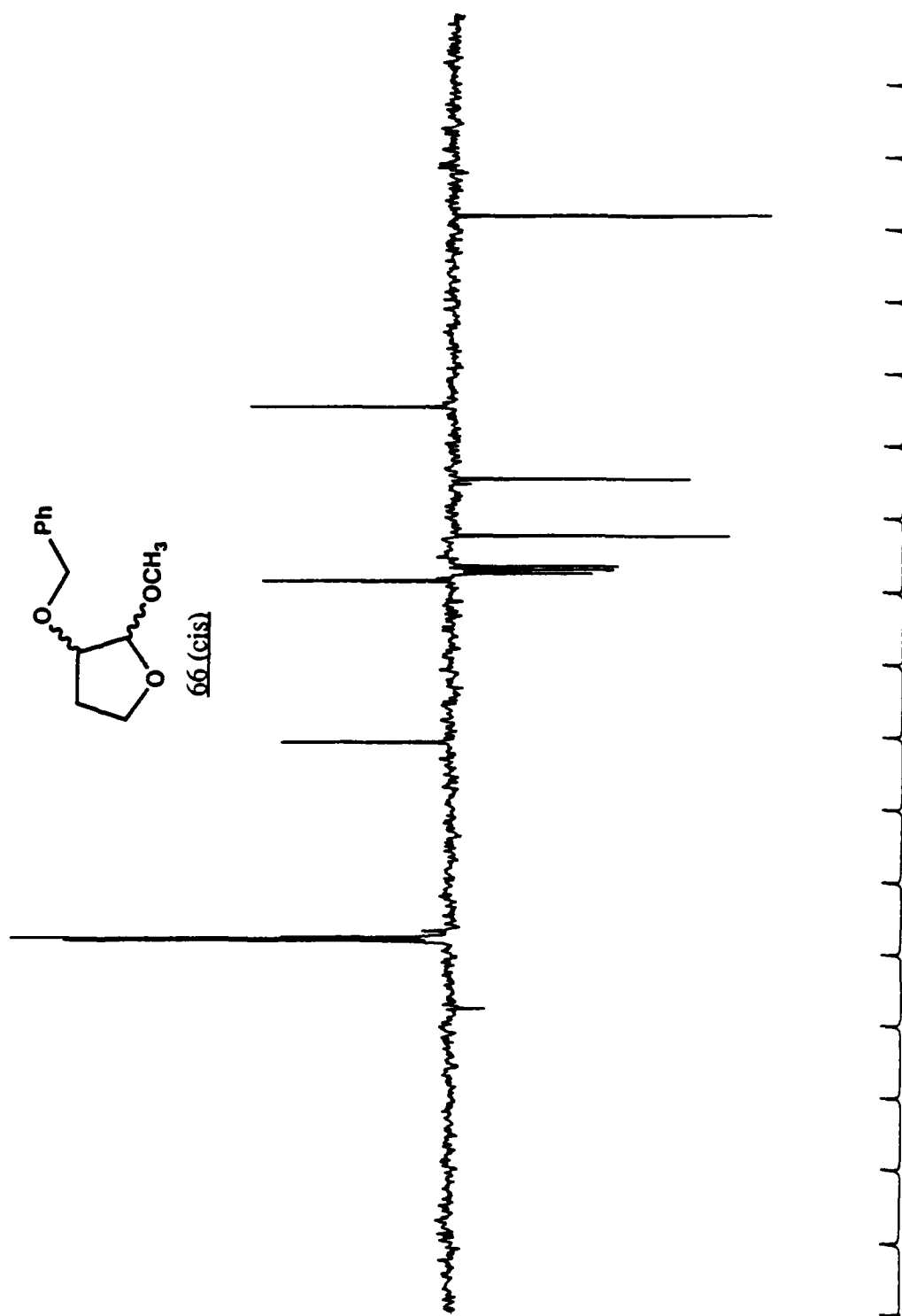


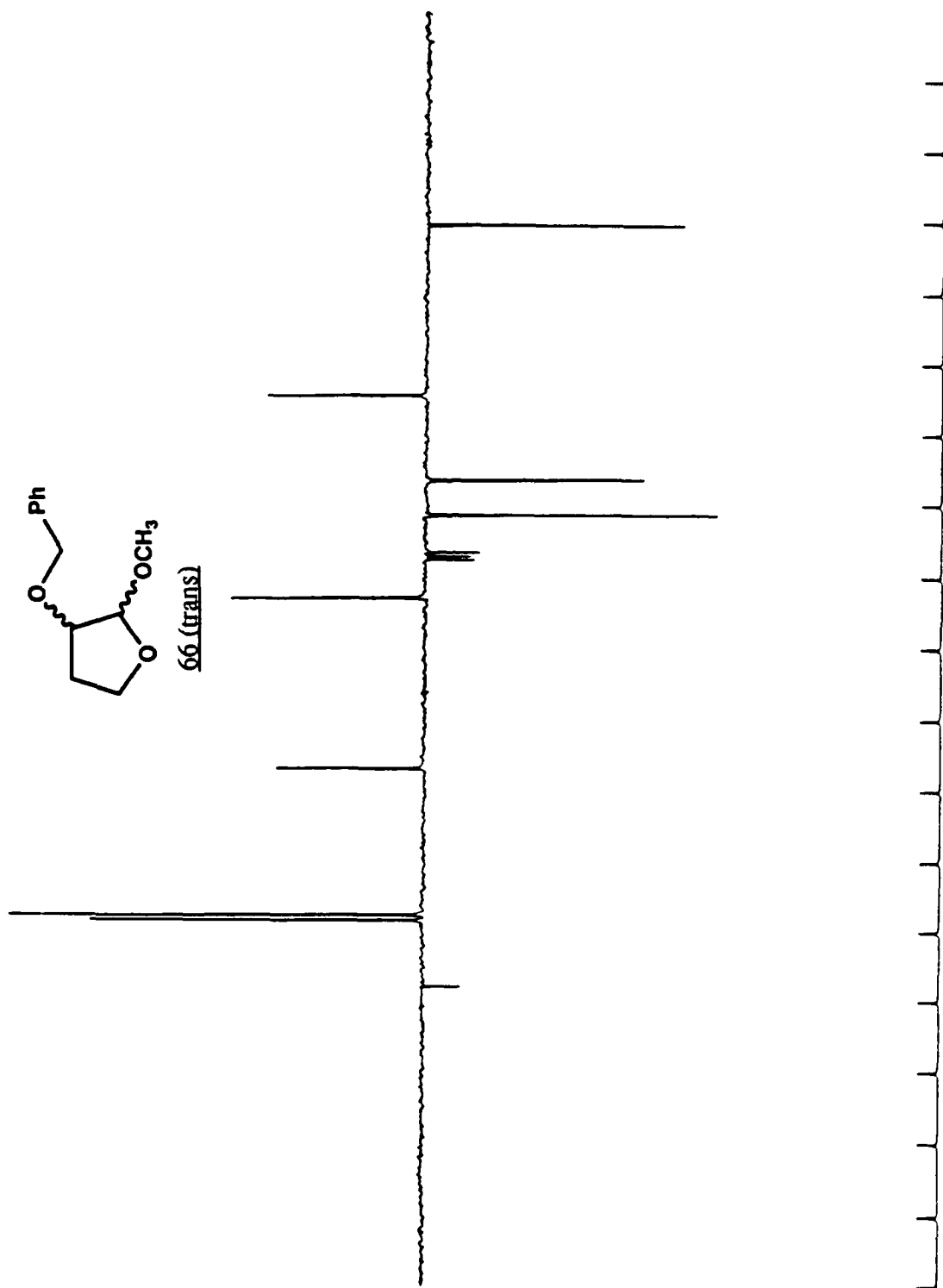


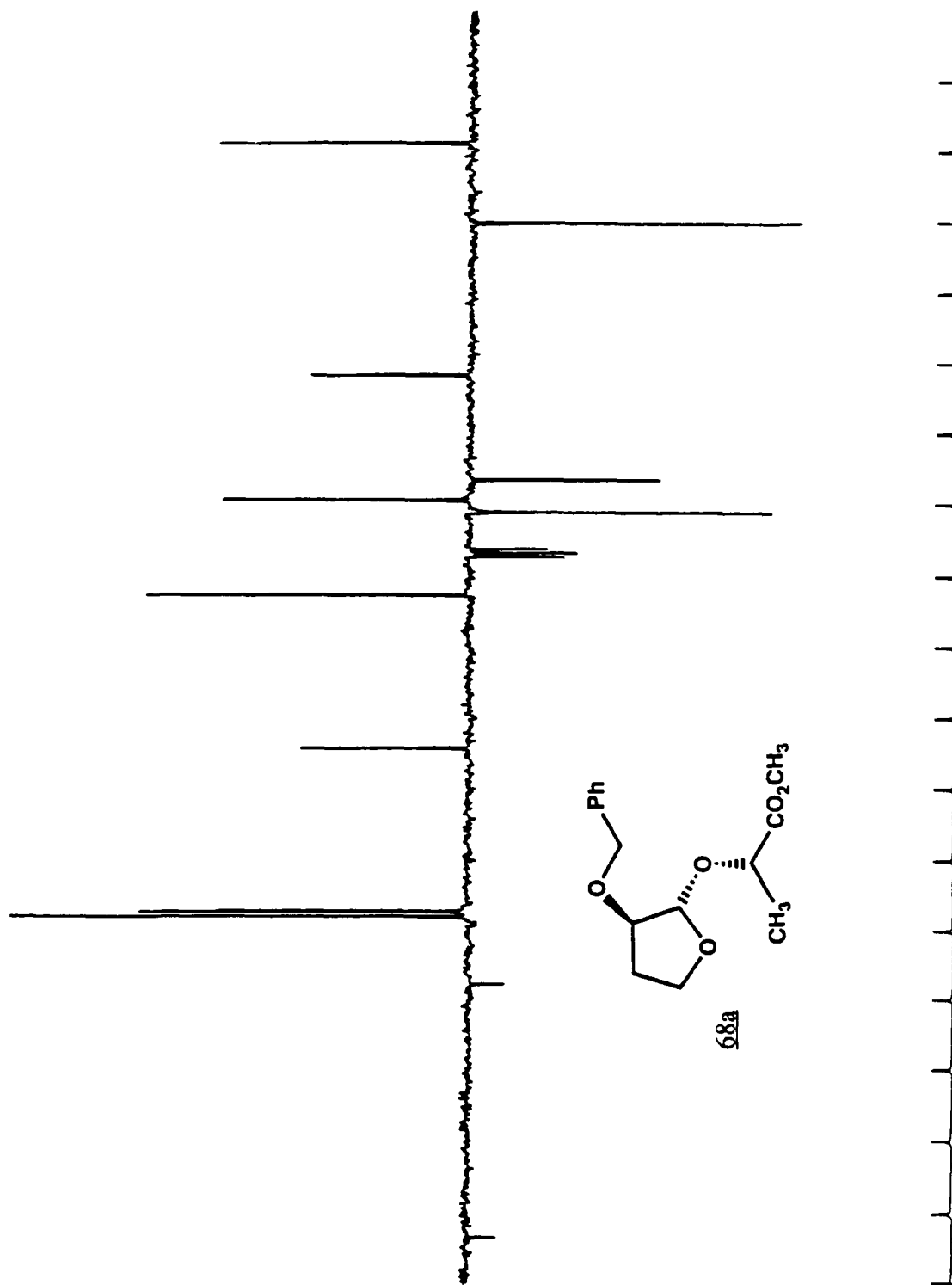


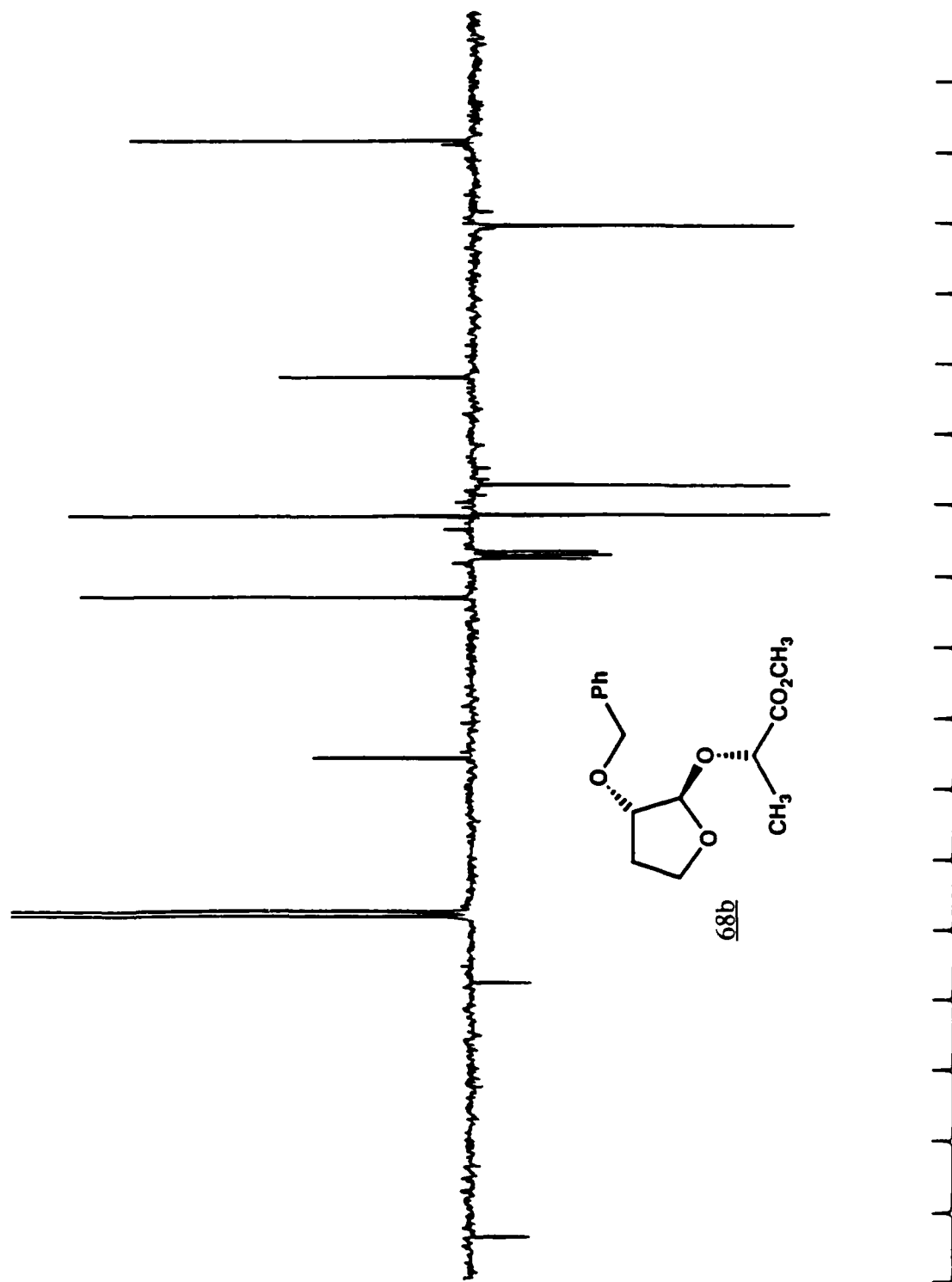


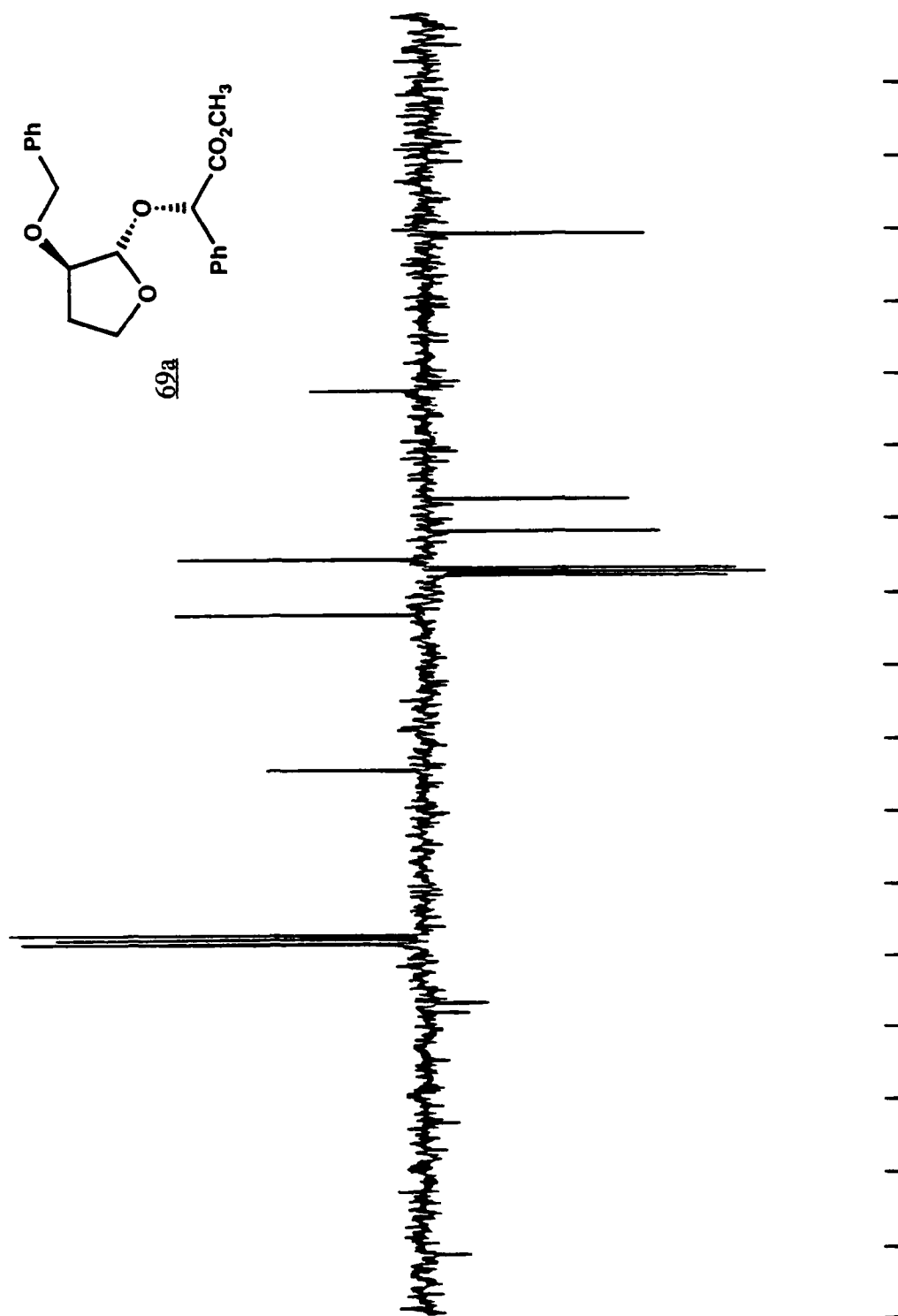


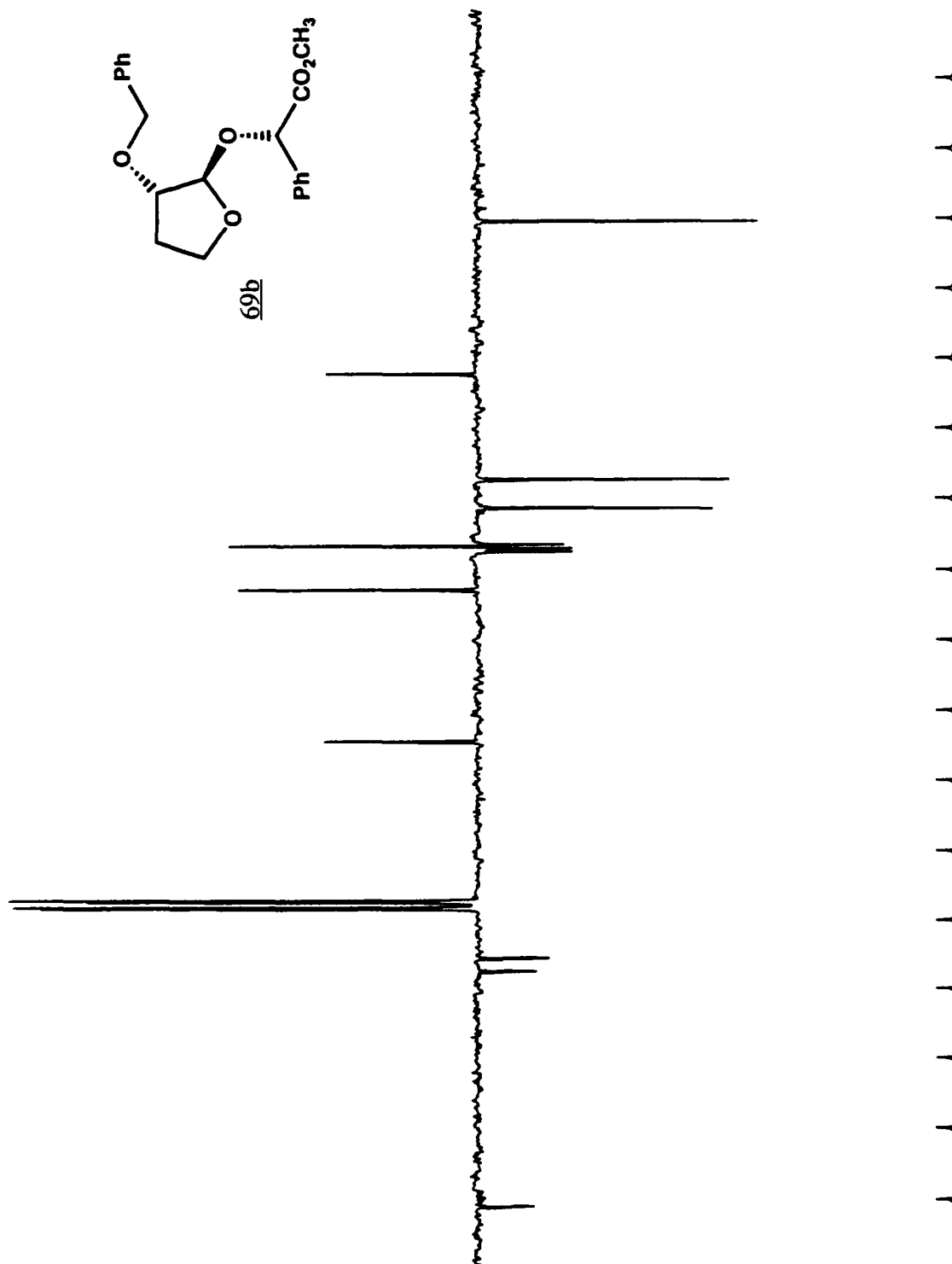


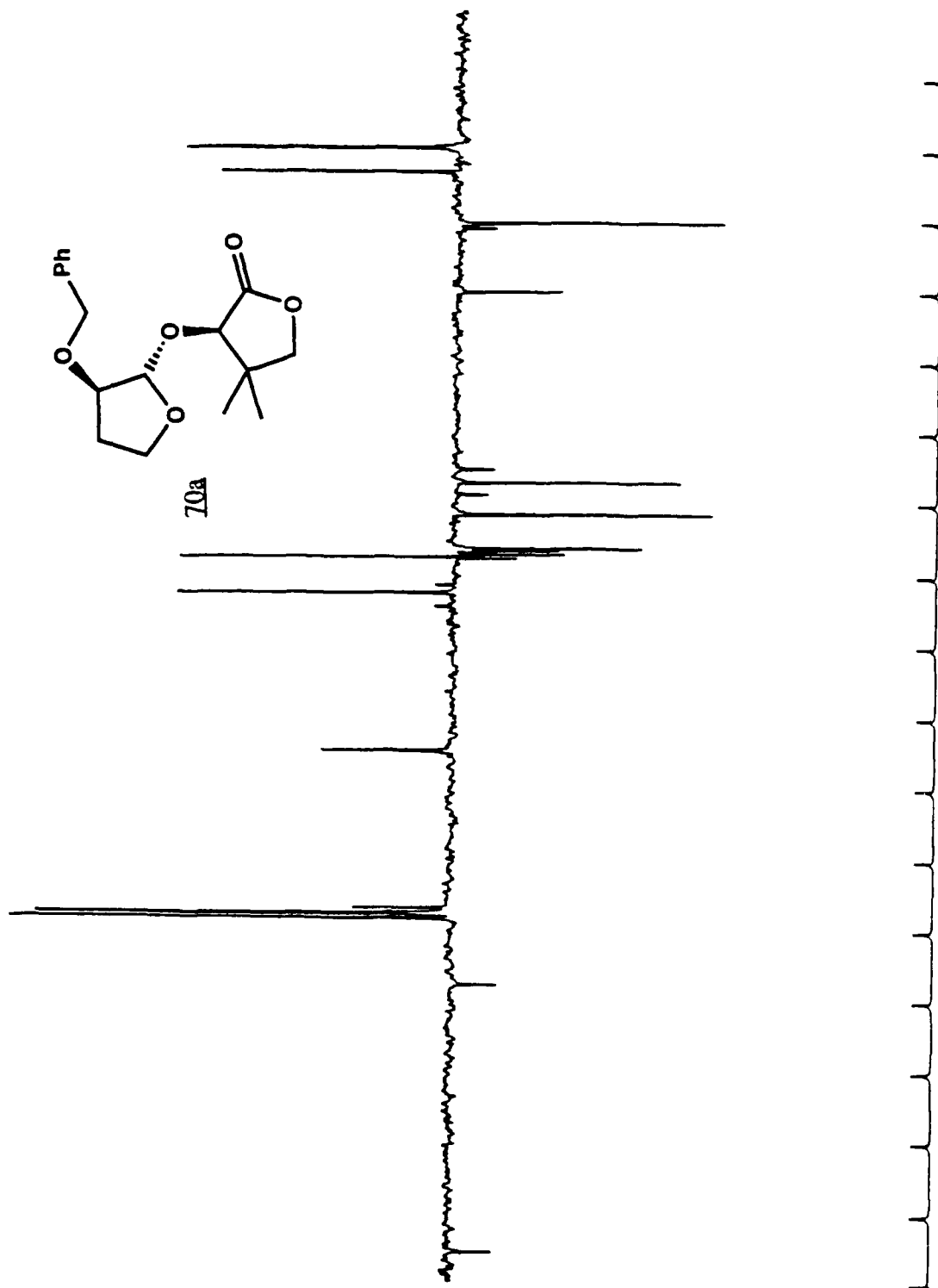


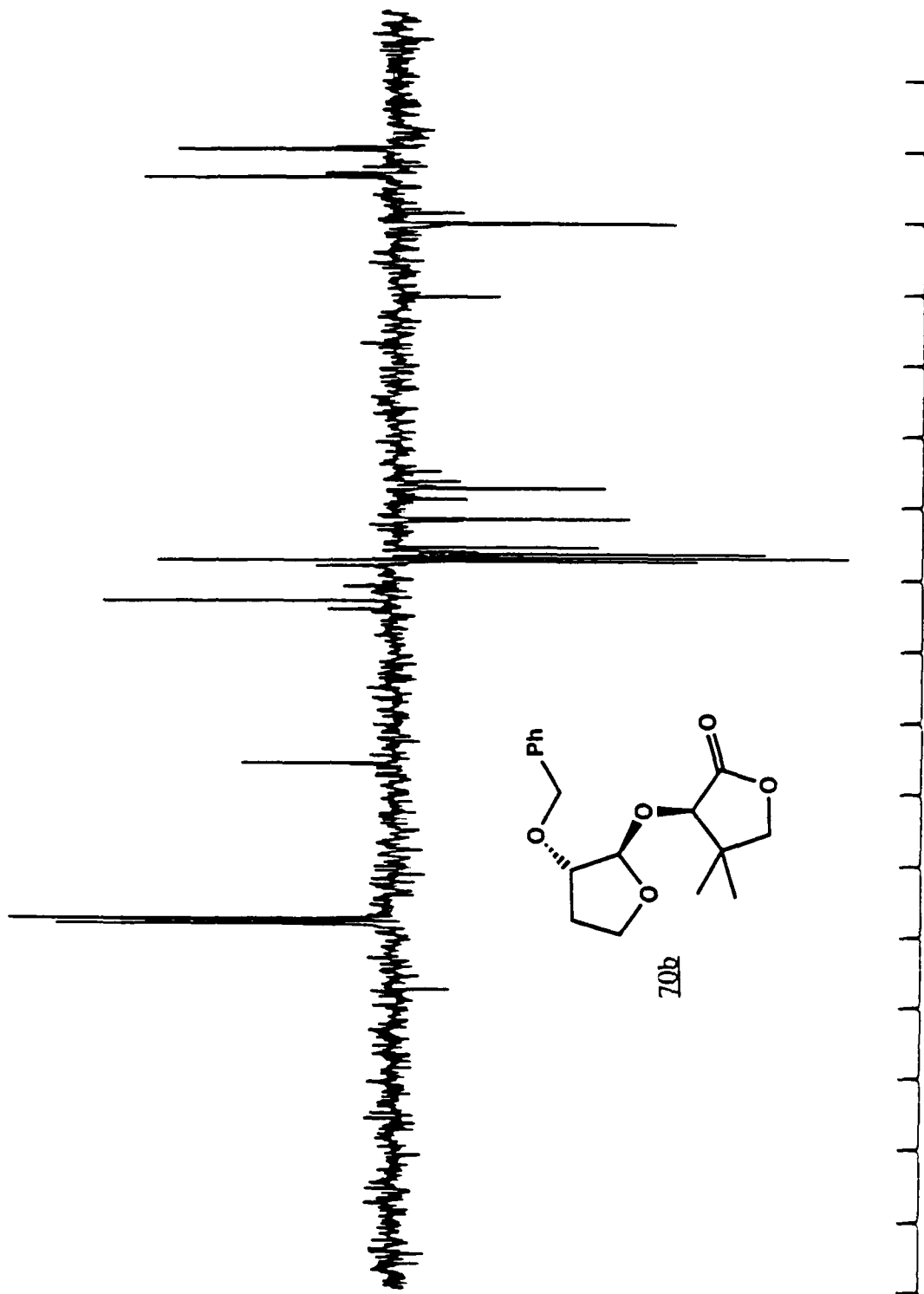


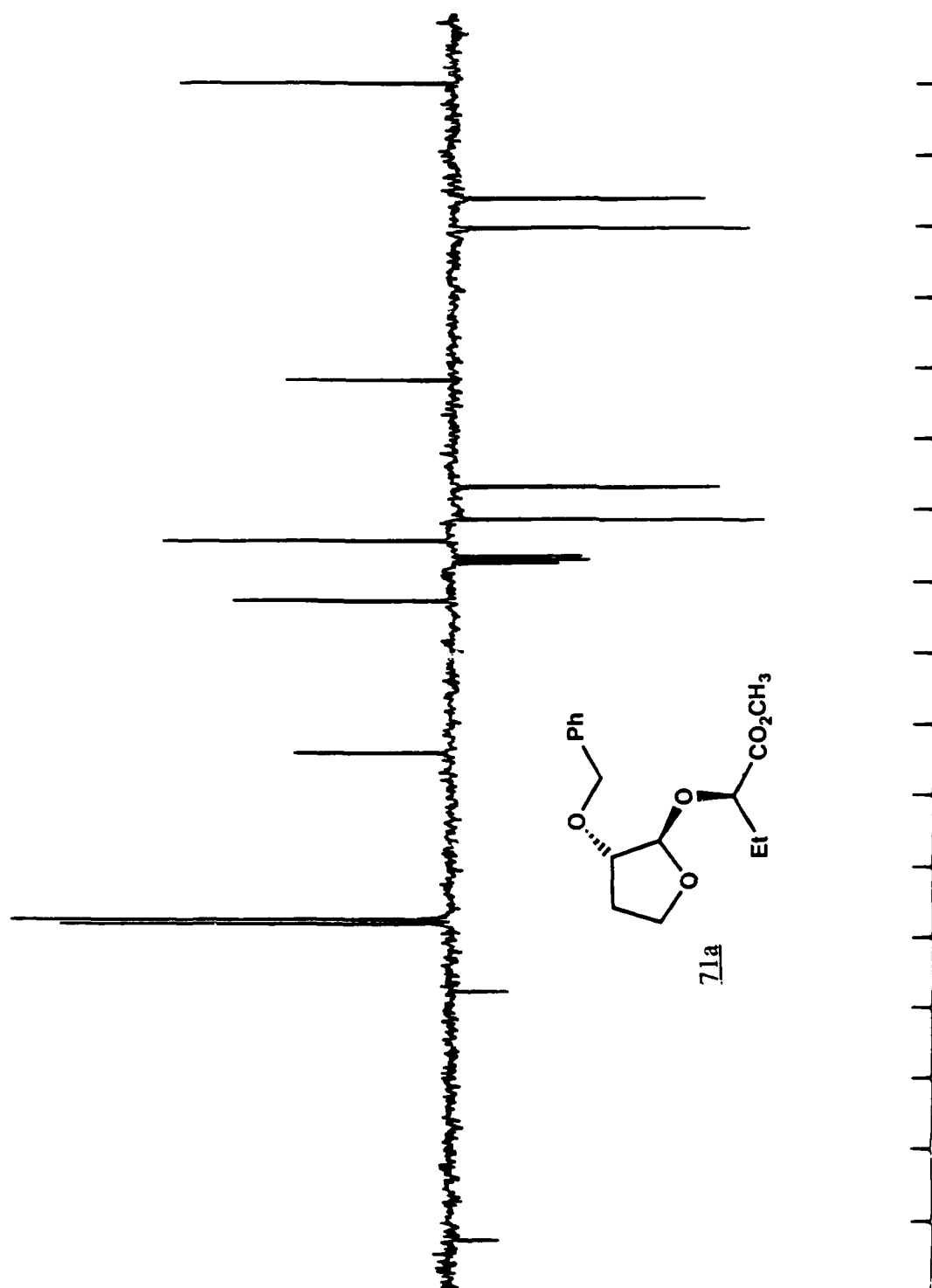


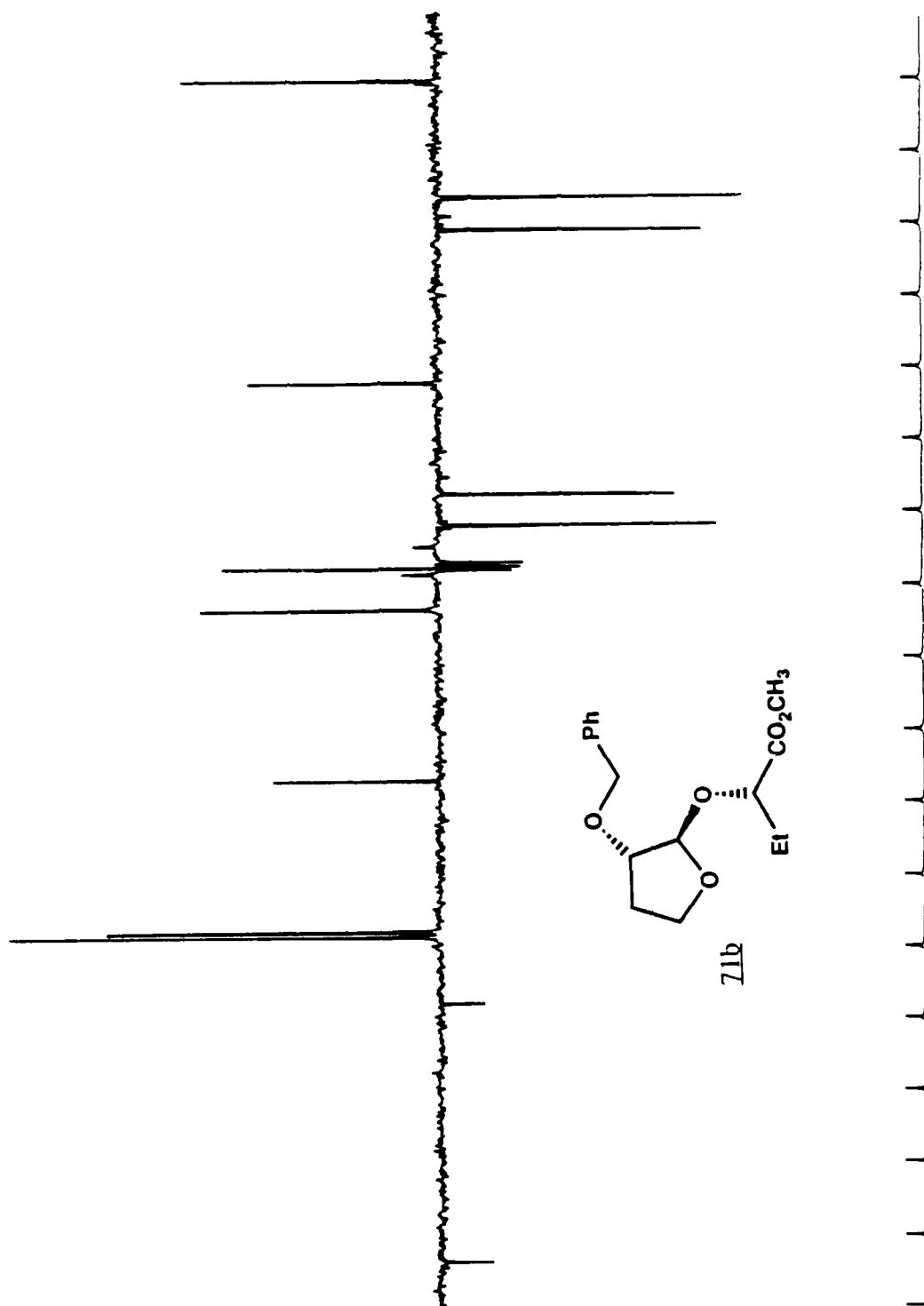


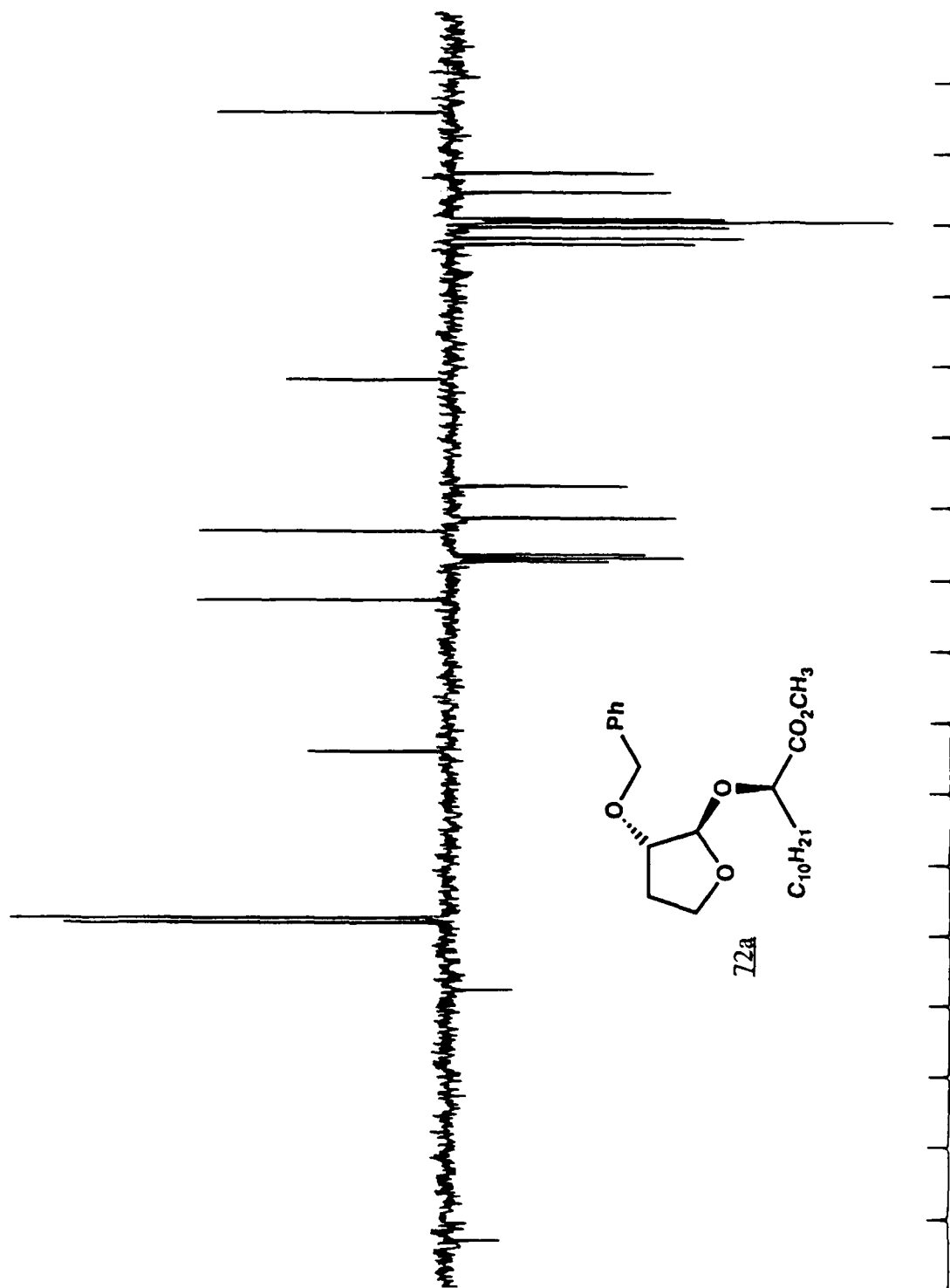


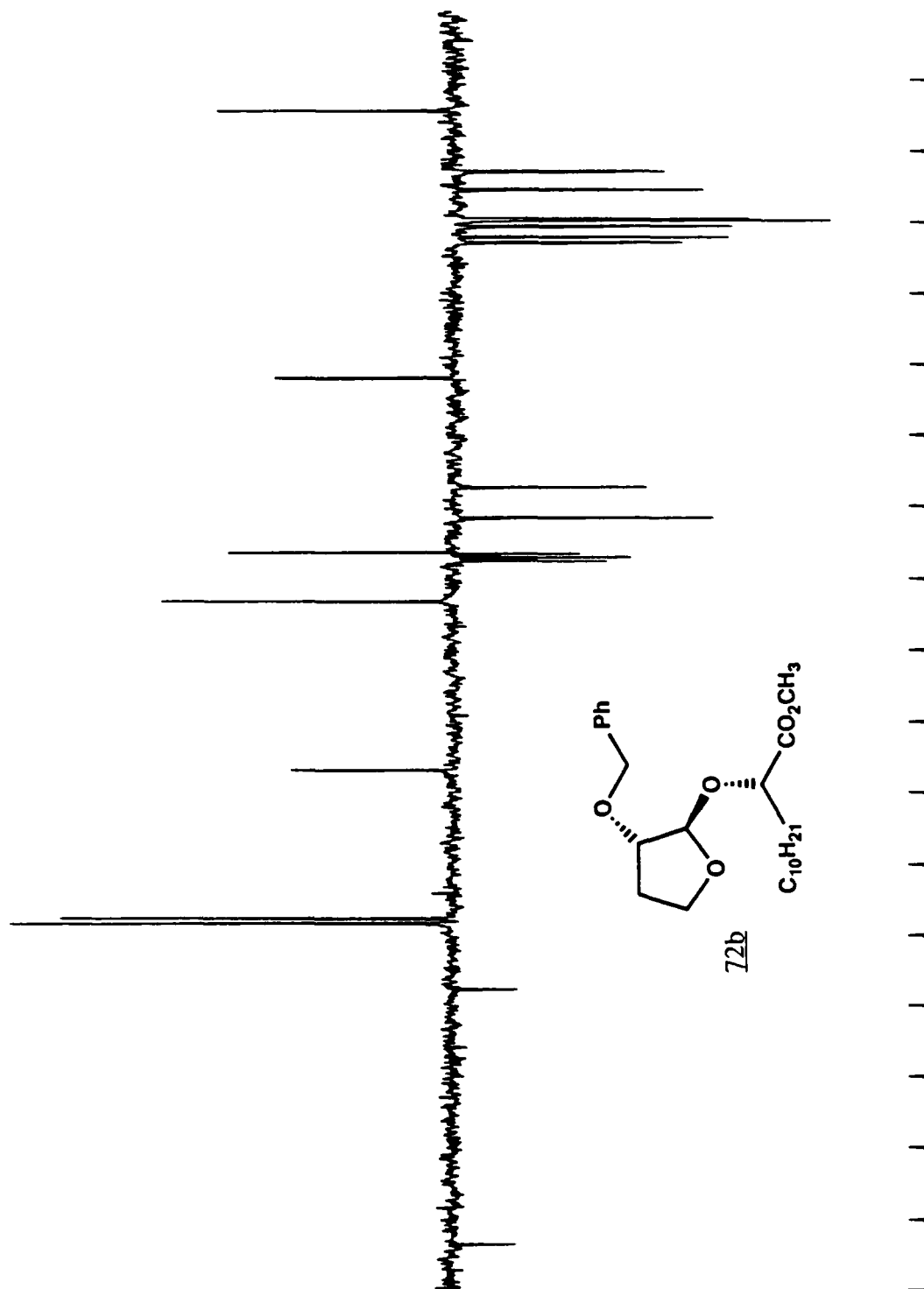


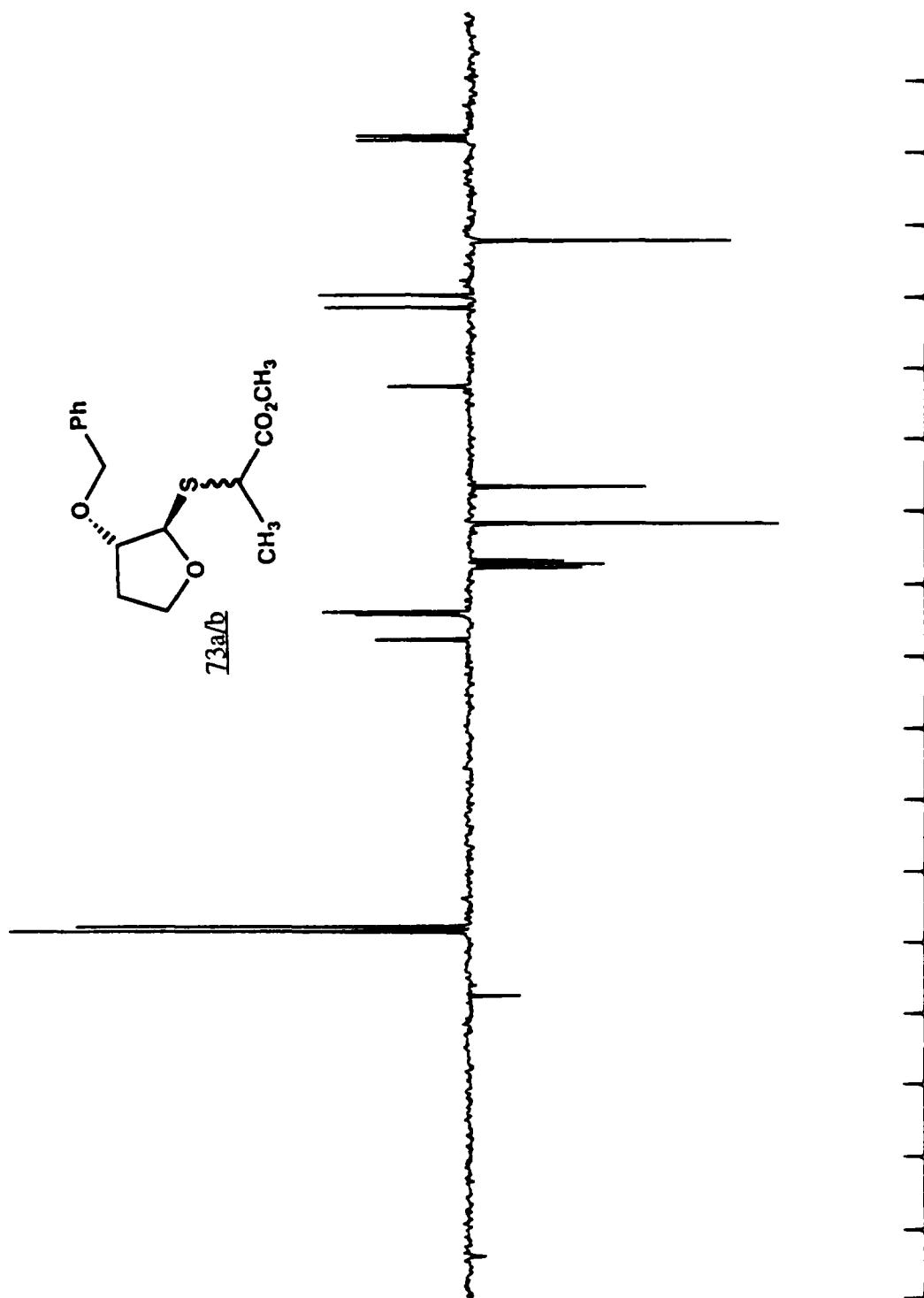












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